

(19) World Intellectual Property Organization
International Bureau



PCT



(43) International Publication Date
23 August 2007 (23.08.2007)

(10) International Publication Number
WO 2007/093051 A1

(51) International Patent Classification:

A61J 1/10 (2006.01) *A61M 5/178* (2006.01)
A61M 5/00 (2006.01) *A61M 5/46* (2006.01)

(21) International Application Number:

PCT/CA2007/000225

(22) International Filing Date:

15 February 2007 (15.02.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2536845 16 February 2006 (16.02.2006) CA
11/355,000 16 February 2006 (16.02.2006) US

(71) Applicant (for all designated States except US): **PKA SOFTTOUCH CORP.** [CA/CA]; 1951 Fiddler's Lane, R.R. #4, Lakefield, Ontario K0L 2H0 (CA).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **MODI, Pankaj** [CA/CA]; 519 Golf Links Road, Ancaster, Ontario L9G 4X6 (CA).

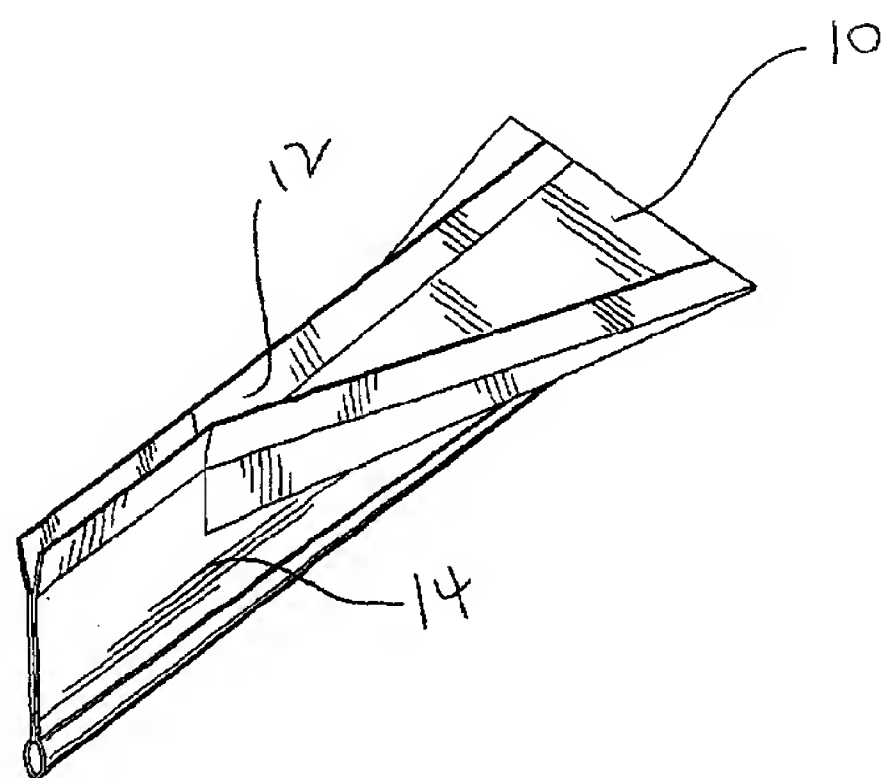
(74) Agent: **MCGUINNESS**, Ursula; Gowling Lafleur Henderson LLP, 1 Main Street West, Hamilton, Ontario L8P 4Z5 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

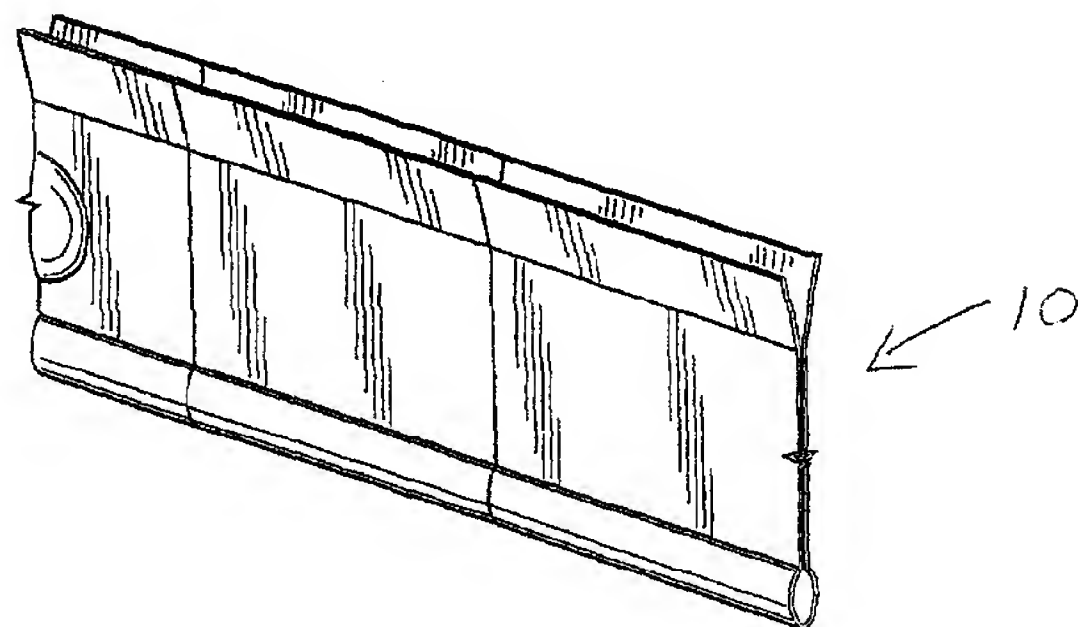
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,

[Continued on next page]

(54) Title: DRUG DELIVERY DEVICE



A



B

(57) Abstract: A novel device and method for intradermal delivery of an active agent is provided. The device comprises a housing which contains a reservoir chamber. A flexible reservoir containing the active agent is placed in the chamber. Upon pressure on an actuator the active agents is delivered via a hollow needle to the skin.

WO 2007/093051 A1



RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

DRUG DELIVERY DEVICE

FIELD OF INVENTION

[0001] The present invention relates to drug delivery devices and methods of delivering a drug intradermally. In particular, the present invention relates to intradermal delivery of a liquid drug.

BACKGROUND OF THE INVENTION

[0002] There has long been a desire to deliver drugs intradermally. The skin comprises two layers, the outer or upper surface called the epidermis, and the internal surface referred to as the dermis. The epidermis does not contain any blood vessels and it is dependent on the underlying dermis for nutrient delivery and waste disposal via diffusion. The inner layer, the dermis, is composed of two layers, the more superficial papillary dermis and the deeper reticular dermis. The papillary dermis is thinner and consists primarily of loose connective tissue containing small capillaries, elastic fibers, reticular fibers and some collagen. The deeper reticular dermis consists of a thicker connective tissue containing larger blood vessels, interlaced elastic fibers and core spindles of collagen fibers arranged in layers parallel to the surface. The reticular layer also contains many antigen-presenting cells, fibroblasts, mast cells, nerve endings, and lymphatics. Because of the high amount of blood vessels, lymphatics and antigen presenting cells in the dermis, this is an ideal site for delivery of drugs and/or antigens.

[0003] A major problem, however, with intradermal delivery is the difficulty in precisely delivering the drug into the dermal layer. Generally, the outer layer, the epidermis, has a thickness of about .05 to 2 mm and the dermis has a thickness between about 1.5 and 4 mm. Thus, to deliver an agent to the dermis, the needle must penetrate the skin to a depth of no more than 5 mm, preferably between about 2 and 4 mm. It is very difficult to control an injection to this shallow depth. For certain types of injection, such as the Mantoux test for tuberculosis, a fine gauge needle is inserted at a 45° angle to try and get the agent into the dermis.

[0004] Several efforts have been made to try and find reliable ways of delivering agents to the dermis. For example, United States Patent Application No. 2005/0124967 is directed to a method for directly delivering a high molecular weight substance into an intradermal space within mammalian skin comprising administering the substance through at least one hollow needle having an outlet with an exposed height between 0 and 1 mm, said outlet being inserted into the skin to a depth of between 0.3 mm and 2 mm, such that delivery of the substance occurs at a depth between 0.3 mm and 2 mm and a microneedle for intradermal injection of a high molecular weight pharmaceutical substance, wherein the microneedle has a length and outlet selected for its suitability for specifically delivering the substance into the dermis.

[0005] United States Patent No. 5,527,288 discloses an intradermal drug delivery device for delivering a liquid drug to a subject via the subject's skin, comprising a housing having a lower surface for application to the skin of the subject; means for affixing the housing in position with the lower surface in contact with the subject's skin; and a drug reservoir within the housing. The reservoir is in the form of an expansible-contractible chamber which is expanded when filled with the drug and which can be contracted to dispense the drug therefrom. A single hollow needle is associated with the drug reservoir and extends through the lower surface, having an inner end communicating with the drug reservoir and an outer end projecting outwards a sufficient distance so as to penetrate through the epidermis and into the dermis when the housing is pressed against the skin. The device also includes means for actively discharging the drug from the reservoir to the subject's skin via the needle.

[0006] United States Patent No. 6,689,118 is directed to a method of making an intradermal injection into the skin of an animal to obtain systemic delivery or to induce an immune response. The method comprises providing a drug delivery device including a needle cannula having a forward needle tip and a needle cannula being in fluid communication with a substance contained in said drug delivery device; inserting the needle tip into the skin of an animal

and engaging the surface of the skin with a skin engaging surface of a limiter portion such that the skin engaging surface of the limiter portion limits penetration of the needle tip into the dermis layer of the skin of the animal; and expelling the substance from the drug deliver device through the needle tip into the skin of the animal to expose the injected substance to the microcirculatory blood vasculature and the lymphatic plexuses.

[0007] United States Patent No. 6,569,143 is directed to another related method of making an intradermal injection comprising providing a drug delivery device; inserting a needle tip into the skin of an animal whereby penetration of the needle tip is limited to the dermis layer of the skin of the animal; and expelling the substance from said drug delivery device through the needle tip into the skin of the animal.

[0008] United States Patent No. 5,997,501 describes an intradermal drug delivery device for the delivery of at least one drug to a subject via the subject's skin. The device comprises a housing having a lower surface; a drug reservoir located with the housing; a cover that is adjustable engaged with the housing from a first extended position to a second retracted position such that the cover is proximal to the lower surface of the housing when the cover is retracted and the cover is distal to the lower surface of the housing when the cover is extended; means for affixing the cover in position with the lower surface of the housing in contact with the subject's skin; a single hollow needle fixed to the cover and having a first end in communication with the drug reservoir and a second end projecting outwards no further than the lower surface of the housing when the cover is extended, and to penetrate through the epidermis and into the dermis when the cover is retracted; and means for actively discharging the drug from the reservoir to the subject's skin via the needle.

[0009] Although multiple efforts have been made to try and provide a device for intradermal delivery, many of the prior art devices are expensive to manufacture or can only be used for one drug. In spite of all the efforts made to provide a method and/or device for intradermal delivery, there remained a need for a reliable, single-use, disposable device for intradermal delivery.

SUMMARY OF THE INVENTION

[0010] Many people consider an injection (at best) unpleasant and (at worst) a painful encounter, no matter how well the nurse or doctor administers the shot. This is because most shots are given subcutaneously or intramuscularly, reaching deep enough into the skin to hit nerves. Part of the skin's job is to sense danger in the environment through nerve cells, and it is richly endowed with these cells – a single square inch of skin contains approximately 1,300 nerve endings. Since most injections are given subcutaneously or intramuscularly, thereby delivering drugs to be absorbed into the blood vessels, the needle generally strikes nerves and causes pain along the way. The device of the present invention is based on a unique technology that allows a liquid pharmaceutical formulation to be delivered into the skin of the patients through a fine needle without the significant pain experienced by regular injection needles. The drug is injected into the layers of the skin, avoiding the pinching of the nerves. This reduces pain significantly or eliminates it totally in many cases thus improving the acceptance and compliance to treat many diseases like diabetes.

[0011] The present invention addresses the problems of the prior art by providing a novel type of reservoir for a drug and a delivery device for delivering the drug from the reservoir to a specific depth of skin. A method of preparing the drug reservoir and a method of delivering a fluid drug are also provided.

[0012] In one aspect of the invention a reservoir for carrying an active agent is provided. The reservoir comprises a fillable bladder having flexible walls that can be sealed.

[0013] A method of manufacturing such a reservoir is also provided. In one embodiment, the method comprises the steps of: opposing two layers of thermoplastic film; heating the film; applying a vacuum mold to the outer surface of each layer of film to form a bubble; and allowing the film to cool.

[0014] In another embodiment, the method comprises preparing a sheet of thermoplastic material having a series of wells or depressions as fillable reservoirs. A top sheet is then applied to seal the reservoirs.

[0015] A method of filling the reservoir is also provided and comprises filling the bladder with a fluid drug; and sealing the reservoir.

[0016] In another aspect of the invention, a device for delivery of a fluid drug to an animal is provided. The term "animal" is used herein to include both human and non-human animals. The devices and methods of the invention are applicable for both human and veterinary use. The device comprises a housing having an upper end and a lower end, the lower end having an aperture therein and the upper end being adapted to receive a drive actuator. A reservoir chamber is disposed within the housing and operatively linked to the drive actuator. The reservoir chamber has a base and wall(s). The wall may be a continuous circular wall or a connected set of walls. Within the reservoir chamber, there is a flexible reservoir filled with the fluid drug. A microneedle is mounted on the base so as to transverse the base of the chamber such that the top of the needle is in communication with the chamber and the tip of the needle extends in the housing below the chamber.

[0017] In a preferred embodiment, the reservoir chamber is located at a predetermined distance from the lower end of the housing whereby abutment of the base of the chamber to the lower end of the housing acts as a stop to provide a predetermined length of travel of the needle through the aperture when the drive mechanism or actuator is activated. The length of travel is optimally set to deliver the drug intradermally. The device also preferably includes biasing means to maintain the reservoir chamber in the upper position within the housing, in the absence of pressure on the actuator thus retaining the needle tip inside the housing.

[0018] In another embodiment of the invention, the device includes a lower housing and an upper housing that fits over the lower housing. In this embodiment, the upper housing is continuous with the actuator that causes the reservoir to descend and contact the needle end.

[0019] In yet another aspect of the invention, a method of administering a fluid drug through the skin of an animal is provided. The method comprises providing a device as defined above; applying the lower surface of the device to the skin; exerting pressure on the drive mechanism thereby lowering the reservoir chamber and causing the needle tip to travel through the aperture and into the skin a predetermined distance; and applying continued pressure on the actuator to cause the upper end of the needle to pierce the reservoir and continuing to apply pressure so that all the contents of the reservoir flow through the needle into the skin.

[0020] This summary of the invention does not necessarily describe all features of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

[0022] Figures 1A to 1G illustrate the steps in the manufacture of a drug reservoir according to the present invention;

[0023] Figures 2A to 2J illustrate the operation of one embodiment of a delivery device of the invention;

[0024] Figures 3A and 3B illustrate another embodiment of a delivery device; and;

[0025] Figures 4A to 4C illustrate yet another embodiment of a delivery device.

DETAILED DESCRIPTION

[0026] The following description is of preferred embodiments.

[0027] In one aspect of the present invention a novel type of drug reservoir is provided. The drug reservoir comprises a fillable bladder. The reservoir is formed between two layers of plastic film. The two layers can be formed from

two sheets or from one sheet folded in half. When two sheets are used, the sheets may comprise the same material, thickness, etc. or they may be two different types of sheets.

[0028] The present invention provides for a drug delivery device incorporating a disposable reservoir. The device may be provided as a single-use, disposable device or a multi-use device. The device comprises a housing that has an upper end and a lower end. As used herein, the term "upper" is used to refer to the surface furthest away from an individual skin and the term "lower" is used to refer to the part of the device that contacts a patient's skin. An actuator is mounted at the top of the housing. The actuator is used to activate a drive mechanism. One example of a drive mechanism is a plunger that travels up and down within the housing. A reservoir chamber is slideably mounted within the housing. The reservoir chamber holds a reservoir filled with a liquid. The reservoir chamber is operatively linked to the drive mechanism. The reservoir chamber has a micro needle mounted on the lower surface of the chamber. When the plunger is depressed, the reservoir housing travels downward within the housing until it stops when the bottom of the reservoir housing hits the bottom of the outer housing.

[0029] A process for the manufacture of one embodiment of the reservoir is shown in Figures 1A-G. In Figure 1A, a sheet of thermoplastic material 10 is folded in half to provide a first surface 12 and a second surface 14. Referring to Figure 1B, the sheet 10 is folded so that the first surface and the second surface overlap each other. Then the sheet is heated to soften the film. Figure 1C illustrates a mold 18 applied to each of the surfaces 12, 14. The mold for each side may be of similar or different shapes. As a vacuum is applied to the mold halves, a bubble 20 is formed and at the same time the boundary 22 of the reservoir shape is sealed. A vertical path 24 is left open for filling of the reservoir. As shown in Figure 1D, the mold halves 18 are removed and the sheet 10 including the bubbles 20 are cooled to room temperature. The filling process is demonstrated in Figure 1E. The film is preferably oriented with the vertical path 24 open at the top for filling to avoid the formation of air pockets during the filling process. A fine dispensing nozzle

26 is inserted into the vertical path 24 and a controlled amount of drug 27 is inserted into the reservoir. The open end 30 of the vertical path 24 is then heat sealed as shown in Figure 1F. The bubble shaped reservoir 20 can then be trimmed as shown in Figure 1G from the remaining sheets of plastic film or the bubble shapes can be partially trimmed and the bubbles can be stored in a roll format.

[0030] In another embodiment, the reservoir is formed by preparing a sheet of material having a series of wells or depressions. The wells are filled with a drug and then an upper sheet is applied to cover and seal the open end of the wells. In both embodiments the reservoir comprises a fillable, sealable bladder of thermoplastic material.

[0031] Various colors and shapes of reservoirs can be used for different drugs. For example, a round, blue bubble may indicate that the reservoir contains insulin and a square pink bubble may indicate a DPT vaccine. The reservoir of the present invention can be used to store many different kinds of active agents. Color coding can be used to identify the agent and/or dose strength.

[0032] The present invention also provides a device and method for delivery of the drug stored in the reservoir to an animal, preferably a human. The device comprises an outer housing. The outer housing can be made of any durable material, preferably a hard plastic. The outer housing can take various shapes, e.g. it can be round, oval, hexagonal, square etc. The outer housing can incorporate various colours to identify the agent and/or dose strength. The outer housing defines an internal chamber that includes an open top at the upper end and a base having an aperture at the lower end. A reservoir chamber is fitted inside the housing. The reservoir chamber is adapted to receive a disposable reservoir such as that described above. A microneedle is mounted in the bottom platform of the reservoir chamber with its upper (non-skin contacting) end protruding upward and just below the reservoir and the skin-contacting tip extending beyond the bottom of the chamber. The reservoir chamber frictionally engages the internal wall(s) of the housing. A drug reservoir or bubble is contained within the reservoir chamber.

A drive actuator is operatively linked to the reservoir chamber. The drive actuator may include a flexible dome or an upper casing. The reservoir chamber typically comprises an open upper end, an internal chamber to hold the reservoir and a base platform with the needle mounted so that it transects the base. A retraction mechanism such as a vacuum bulb or a spring is also optionally included.

[0033] In use, the delivery device is placed on the skin with the lower end of the housing touching the skin. The drive mechanism is then actuated to drive the reservoir chamber downwards until the base platform of the reservoir chamber hits the base of the housing. This causes the needle to exit through the aperture in the base of the housing a predetermined distance and enter into the skin to a predetermined depth. Further downward pressure on the plunger compresses the drug filled reservoir and causes it to be pierced by the upper end of the needle. This puts the cannula of the needle in fluid communication with the contents of the reservoir and as the downward pressure continues until the tip of the plunger bottoms on the base platform of the reservoir chamber, the contents of the reservoir are passed through the cannula of the needle to the skin of an animal or human subject. When the pressure on the drive mechanism is released, retraction means cause the needle to be retracted back into the housing for disposal.

[0034] One preferred embodiment of the device and its operation is shown in Figures 2A-J. The device 50 comprises housing 52. The housing has an open upper end 54 and a bottom base 56 defining an interior chamber 58 that optionally includes a spring. The bottom base comprises an aperture 60. The interior of the housing is adapted to receive a reservoir chamber 62. The reservoir chamber comprises a base 64 and a surrounding wall 66 extending upwards from the base defining a chamber 62 with an open top 68. A filled reservoir body 70 is located in the reservoir chamber.

[0035] A single hollow needle 72 is associated with the reservoir chamber 62. The needle 72 extends through the base 64 of the chamber 62 and has a cannula with an upper end 74 communicating with the interior 75 of the reservoir chamber and a lower end 78 projecting out of the chamber and

down a predetermined distance. The open top 68 of the reservoir chamber is adapted to receive an actuator 80. In the illustrated embodiment, the actuator comprises a plunger 82 having an activation flange 84 at one end and a stopper 86 at the other end. In the initial position of the device as provided and as shown in Figures 2A and 2B, the base 64 of the reservoir chamber 62 is held at a predetermined distance from the interior surface 88 of the base 56 of the housing by at least one releasable latch 90 which retains the chamber in position by the interaction of the latch 90 with a latch retainer 92. The latch 90 includes a notch 91.

[0036] In one preferred embodiment an upper housing 96 encases the plunger 80.

[0037] It is clearly apparent that the distance the needle travels can be varied depending on the desired application and on the bubble position and the length of the needle. For example, the device can be adapted to have the needle travel a distance between about 0.5 mm to about 10 mm. Thus, the device of the invention can be adapted for intradermal, subcutaneous or intramuscular injections. The needle preferably travels from about 3 mm to 8 mm. The needle gauge is preferably 25 to 84 gauge although different gauge needles can be used.

[0038] The operation of the device is illustrated sequentially in Figures 2A to 2J. Figures 2A and 2B illustrate the device in the initial state as described above. Referring now to Figures 2C and 2D for use, the base 56 of the housing 52 is placed against the skin. When pressure is exerted on the actuator 80, the latch 90 is released from the retainer 92. The actuator 80 is connected to the reservoir chamber 62 via a notch 100 and tab 102 connector and the reservoir chamber will be forced down until the base 64 of the reservoir chamber 62 hits the interior surface 88 of the housing base 56 and the chamber is stopped from any further downward movement. By adjusting the relative sizes and positions of the components, the length of the travel of the needle through the aperture into the skin can be tightly controlled. The distance that the needle extends is about 0.5 to 10 mm, preferably 0.5 to 5 mm, more preferably from about 3 mm to about 5 mm, even more preferably

from about 1.5 to 3 mm. The outer layer of skin, the epidermis typically has a thickness of about .5 to 2 mm. and the inner layer, the dermis, has a thickness of about 1.5 to 3 mm. The dermis comprises two layers, the papillary layer and the reticular layer. The reticular layer contains many blood vessels and lymph vessels, making it a desirable area for delivery of active agents. Below the dermis is the subcutaneous layer and then muscle. In a preferred embodiment, the distance that the tip of the needle can extend beyond the lower outer surface of the housing is selected to be optimum for insertion in the dermis or subcutaneous layer. As the reservoir chamber 62, carrying the needle 72 descends, the lower tip of the needle 78 exits the aperture 60. The downward travel of the reservoir chamber 62 is limited when the base 64 of the chamber contacts the base 56 of the housing. In this way the travel of the needle through the aperture 60 is also limited so as to limit the depth of penetration of the needle into the skin. The components of the device have been configured so that the distance that the bottom of the chamber travels is translated into a predetermined travel for the needle through the aperture in the bottom of the housing to provide a certain skin penetration.

[0039] Referring now to Figures 2E and 2F, as continued pressure is applied to the actuator 80, the tab 102 is released from the notch 100 and the plunger 82 descends within the reservoir chamber forcing the filled reservoir 70 downwards until it contacts the base 64 of the reservoir chamber 62. As the actuator 80 exerts pressure on the reservoir 70, the reservoir 70 contacts the upper end 74 of the needle 72 and is punctured. The cannula of the needle 72 is now in fluid communication with the contents of the reservoir.

[0040] Referring now to Figures 2G and 2H, continued pressure on the actuator 80 compresses the reservoir 70 and forces all the contents to flow through the needle 72 and into the patient. The downward travel of the actuator 80 is stopped when the plunger stopper 86 contacts the base 64 of the reservoir chamber 62.

[0041] After use, the needle is preferably retracted back into the housing 52 as illustrated in Figures 2I and 2J. The position of the reservoir chamber 62

carrying the needle 72 is preferably biased to the pre-activation position by biasing means such as a spring, a vacuum bulb or a moldable bulb. Once pressure is released on the actuator 80, the base 64 of the reservoir chamber moves up in the housing thus automatically retracting the used needle into the housing. This provides for safe disposal of the device. In a preferred embodiment, the needle is preferably locked in the retracted position. Figure 2J shows a retracted reservoir chamber that is locked in position when tab 102 slides into indent 104.

[0042] In the embodiment illustrated in Figures 3A and 3B, an actuator 106 is continuous with an upper casing 108 that fits over a housing 110. The housing 110 receives a reservoir chamber 112 that has a needle 114 transversely mounted through its base 116. A drug reservoir 118 is contained within the chamber 112. As shown in Figure 3B, pressure on the actuator 106 causes the reservoir chamber 112 to descend until it abuts the base 120 of the housing 110. As the chamber 112 descends, it drives the tip 122 of the needle 114 through an aperture 124 in the housing 110. Further pressure causes the rear 126 of the needle to puncture the reservoir 118. Upon continued pressure, the contents of the reservoir are expelled through the needle.

[0043] In another embodiment, a flexible dome fits over the plunger rod and activation flange. It is also clearly apparent the manual activation flange can be exposed. The device also optionally includes a spring that is located around or below the reservoir chamber base such that when pressure on the activation flange is released the compressive energy of the spring causes the needle to be retracted back into the housing.

[0044] Figures 4A to 4C illustrate another embodiment of the device. The device 130 includes a housing 132 and an upper casing 134. An actuator 136 is operably linked to a reservoir chamber 138 disposed within the housing 132. For use, a drug filled reservoir 140 is placed in the reservoir chamber 138. A needle 142 is mounted so as to transverse the base 144 of the chamber 138. The device also includes a spring 146 that biases the reservoir chamber 138 upwards in the housing 132. Upon pressure on the actuator

136, the spring compresses and the reservoir chamber travels downward carrying the needle and the needle tip 148 exits the housing 132. Upon further pressure, the actuator 136 compresses the drug filled reservoir 140 until the back 150 of the needle punctures the reservoir and the contents flow through the needle as shown in Figure 4C.

[0045] In another aspect of the invention, a method for delivering an effective amount of a liquid active agent to an animal, preferably a human, is provided. The method comprises providing a drug delivery device according to the present invention, said device containing a reservoir filled with the desired drug; applying the bottom surface of the drug delivery device of the invention to the skin of an animal, applying pressure on the actuator to cause the needle to enter the skin, applying continued pressure to puncture the reservoir and deliver the contents of the reservoir through the cannula of the needle.

[0046] The device of the present invention can be used to deliver a variety of active agents. The term "drug" is used loosely herein to refer to prophylactic as well as therapeutic agents. For example, vaccines may be delivered using the device. In addition, the term refers broadly to active agents, such as nucleic acids, small molecules, therapeutic proteins, hormones, analgesics, etc. in addition to traditional pharmacologic agents. Typical drugs include peptides, proteins or hormones such as insulin, calcitonin, calcitonin gene regulating protein, atrial natriuretic protein, colony stimulating factor, betaseton, erythropoietin (EPO), interferons such as α , β , or γ interferon, somatropin, somatotropin, somatostatin, insulin-like growth factor (somatomedins), luteinizing hormone releasing hormone (LHRH), tissue plasminogen activator (TPA), growth hormone release hormone (GHRH), oxytocin, estradiol, growth hormones, leuprolide acetate, factor VIII, interleukins such as interleukin-2, and analogues thereof; analgesics such as fentanyl, sufentanil, butorphanol, buprenorphine, levorphanol, morphine, hydromorphone, hydrocodone, oxycodone, methadone, lidocaine, bupivacaine, diclofenac, naproxen, pargafen, and analogues thereof; anti-migraine agents such as sumatriptan, ergot alkaloids, and analogues thereof,

anti-coagulant agents such as heparin, hirudin, and analogues thereof; anti-emetic agents such as scopolamine, ondansetron, domperidone, metoclopramide, and analogues thereof; cardiovascular agents, anti-hypertensive agents and vasodilator such as diltiazem, clonidine, nifedipine, verapamil, isosorbide-5-mononitrate, organic nitrates, agents used in treatment of heart disorders, and analogues thereof; sedatives such as benzodiazepines, phenothiazines, and analogues thereof; narcotic antagonists such as naltrexone, naloxone, and analogues thereof; chelating agents such as deferoxamine, and analogues thereof; anti-diuretic agents such as desmopressin, vasopressin, and analogues thereof; antineoplastics such as 5-fluorouracil, bleomycin, and analogues thereof; prostaglandins and analogues thereof; and chemotherapy agents such as vincristine, and analogues thereof. Stabilized preparations of drugs that can be stored at room temperature are particularly preferred for use in the device and method.

[0047] The term "fluid" refers to any fluid containing an active agent or communication of agents that can pass through the cannula of the microneedle. This includes a liquid, a solution, a gel, a dispersion or a fine suspension.

[0048] All citations are hereby incorporated by reference.

[0049] The present invention has been described with regard to one or more embodiments. However, it will be apparent to persons skilled in the art that a number of variations and modifications can be made without departing from the scope of the invention as defined in the claims.

WHAT IS CLAIMED IS:

1. A reservoir for carrying an active agent, said reservoir comprising a fillable bladder of thermoplastic material.
2. A reservoir according to claim 1, wherein the reservoir is color coded to a specific drug.
3. A reservoir according to claim 1, wherein the bladder has a capacity of about 0.2 to 10 ml.
4. A reservoir according to claim 3, wherein the bladder has a capacity of about 0.3 to 6 ml.
5. A reservoir according to claim 4, wherein the bladder has a capacity of about 0.5 to 3 ml.
6. A method of manufacturing a reservoir as defined in claim 1, comprising the steps of:
 - i. providing at least one sheet having a depression formed therein and facing that sheet with a second sheet.
7. A method according to claim 6, further comprising the steps of:
 - i. filling the bubble with a fluid drug; and
 - ii. sealing the bubble.
8. A device for delivery of a fluid drug to an animal, said device comprising:
 - i. a housing having an upper end and a lower end, said lower end having an aperture therein and said upper end being associated with an actuator;
 - ii. a reservoir chamber disposed within the housing and operatively linked to the actuator, said reservoir chamber comprising a base and wall(s);
 - iii. a flexible reservoir, filled with the fluid drug, disposed within the reservoir chamber; and
 - iv. a needle mounted so as to transverse the base of said chamber such that a back of the needle is in communication with the chamber and a tip of the needle extends in the housing below the chamber.
9. A device according to claim 8, wherein the reservoir chamber is

located at a predetermined distance from the lower end of the housing whereby abutment of the base of the chamber to the lower end of the housing acts as a stop to provide a predetermined length of travel of the needle through the aperture when the actuator is activated.

10. A device according to claim 9, wherein the length of travel of the needle is from about 0.5 mm to about 10 mm.
11. A device according to claim 9, wherein the length of travel of the needle is from about 1.5 mm to about 8 mm.
12. A device according to claim 9, wherein the length of travel of the needle is from about 3 mm to about 8 mm.
13. A device according to claim 8 wherein the actuator is a plunger comprising a plunger rod having an activation flange at one end and a stopper at the other end.
14. A device according to claim 8 further comprising biasing means to retain the needle with the housing in the absence of pressure on the drive mechanism.
15. A device according to claim 14 wherein the biasing means comprises an air bladder.
16. A device according to claim 14 wherein the biasing means comprises a spring.
17. A device according to claim 16 wherein the spring is disposed below the base of the reservoir chamber.
18. A device according to claim 16, wherein the spring is associated with the actuator.
19. A device according to claim 8 further including a piercable septum covering said aperture.
20. A method of administering a fluid drug through the skin of an animal, said method comprising:
 - i. providing a device as defined in claim 8;
 - ii. applying the lower surface of the device to the skin;
 - iii. exerting pressure on the drive mechanism thereby lowering the reservoir chamber and causing the needle

tip to travel through the aperture and into the skin a predetermined distance; and

- iv. applying continued pressure on the drive mechanism to cause the upper end of the needle to pierce the reservoir and the contents of the reservoir to flow through the needle into the skin.

21. A method according to claim 20 wherein the tip of needle is limited to travel a depth of 1.5 to 8 mm.

22. A method according to claim 20 wherein the needle travel is from about 1.5 to 3 mm.

23. A method according to claim 20 wherein the needle travel is from about 3 to 5 mm.

24. A method according to claim 20 wherein the needle travel is from about 5 to 8 mm.

25. A method according to claim 20 further comprising the step of retracting the needle back into the housing after use.

26. A method according to claim 25 whereby the step of retracting is done by biasing means automatically upon release of pressure on the drive mechanism.

27. A device for delivering an active agent to the skin, said device comprising:

- i. a housing;
- ii. a reservoir chamber releasably positioned in said housing, said reservoir chamber adapted to receive a reservoir containing the active agent;
- iii. at least one needle having an upper opening and a lower opening defining a cannula transversing the base of the reservoir chamber; and
- iv. actuator means for moving said chamber downward within said housing,

28. A device according to claim 27, wherein said reservoir chamber further comprises latch means for retaining said chamber in an upward position in the housing, said latch means adapted for

release upon downward pressure on the actuator.

29. A device according to claim 28, wherein said latch means includes a tab and notch for connection to the actuator.
30. A device according to claim 29, wherein said actuator includes at least one notch for receiving a tab on said latch means.
31. A device according to claim 29, wherein said actuator includes an upper notch and a lower notch.
32. A device according to claim 29, wherein said upper notch receives said tab to lock said needle in a retracted position.

1/12

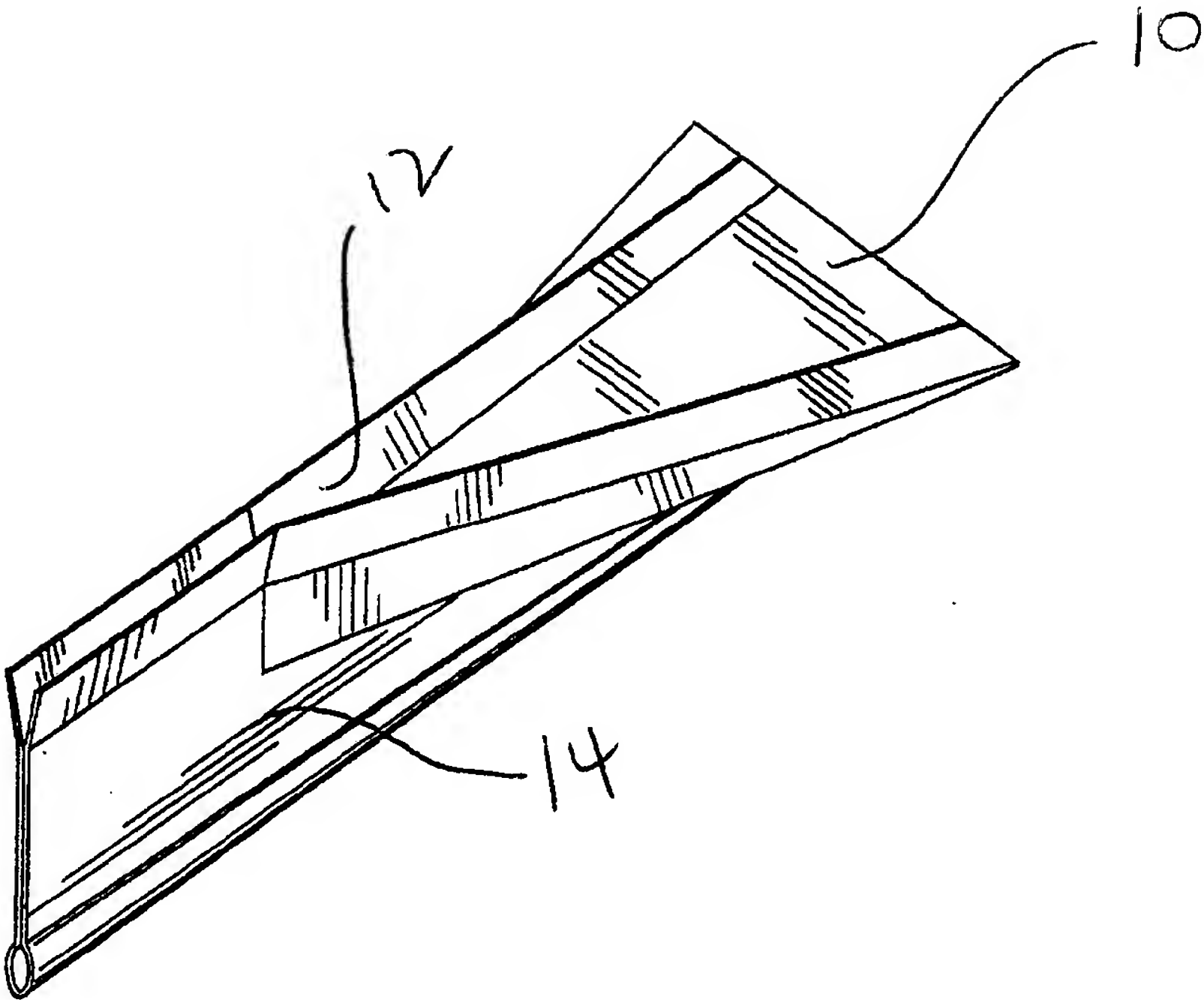


FIG. 1A

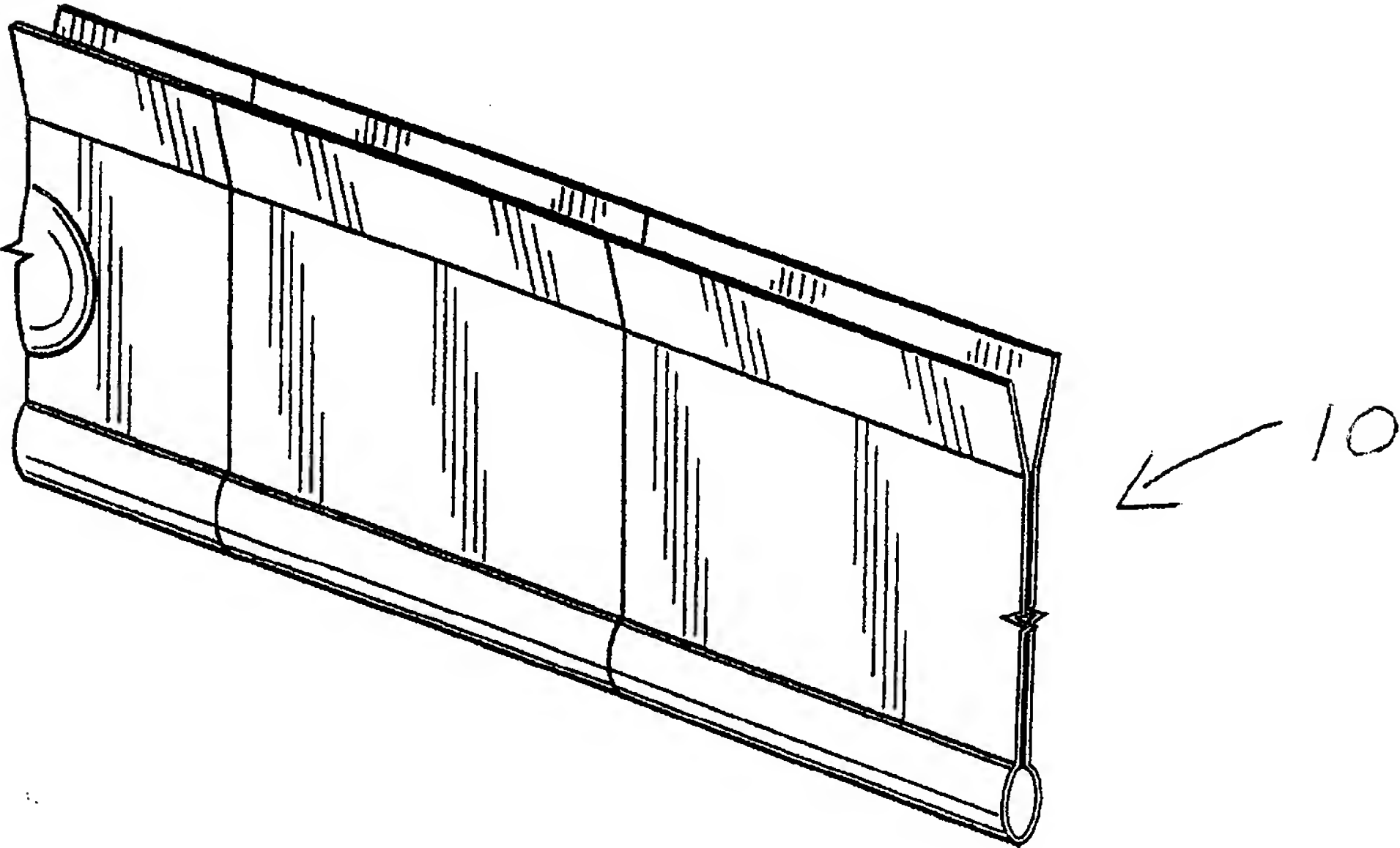
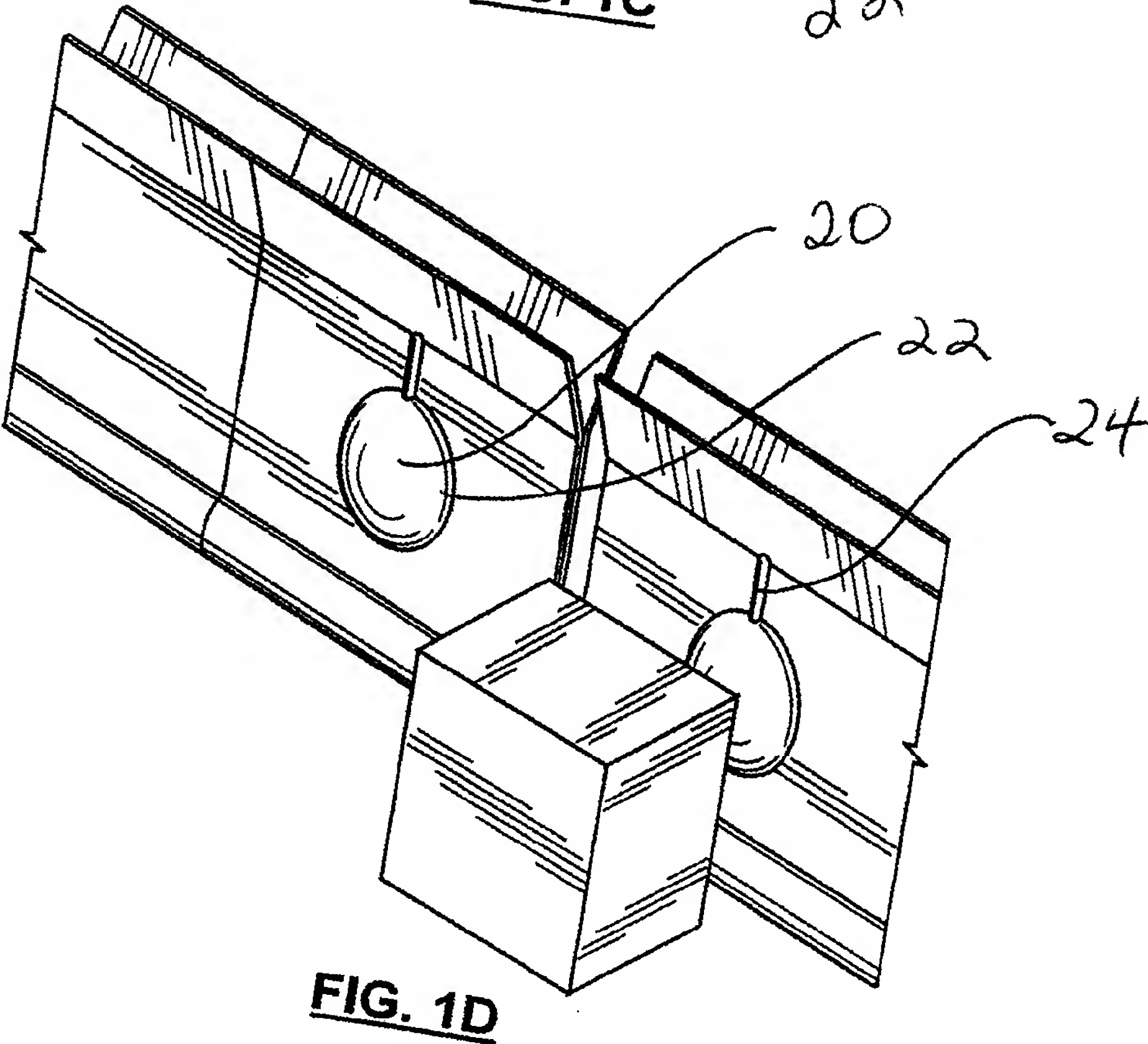
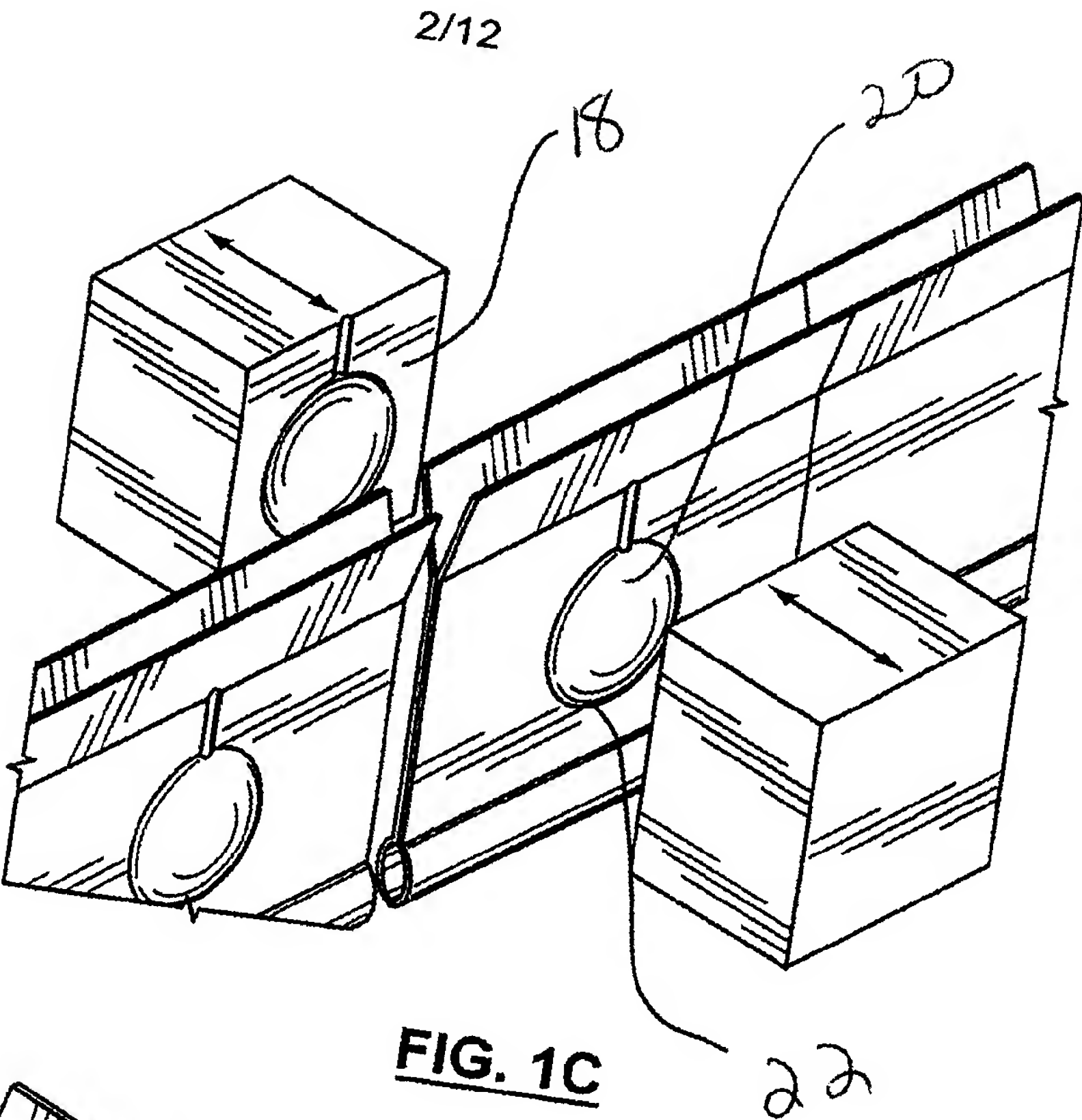


FIG. 1B



3/12

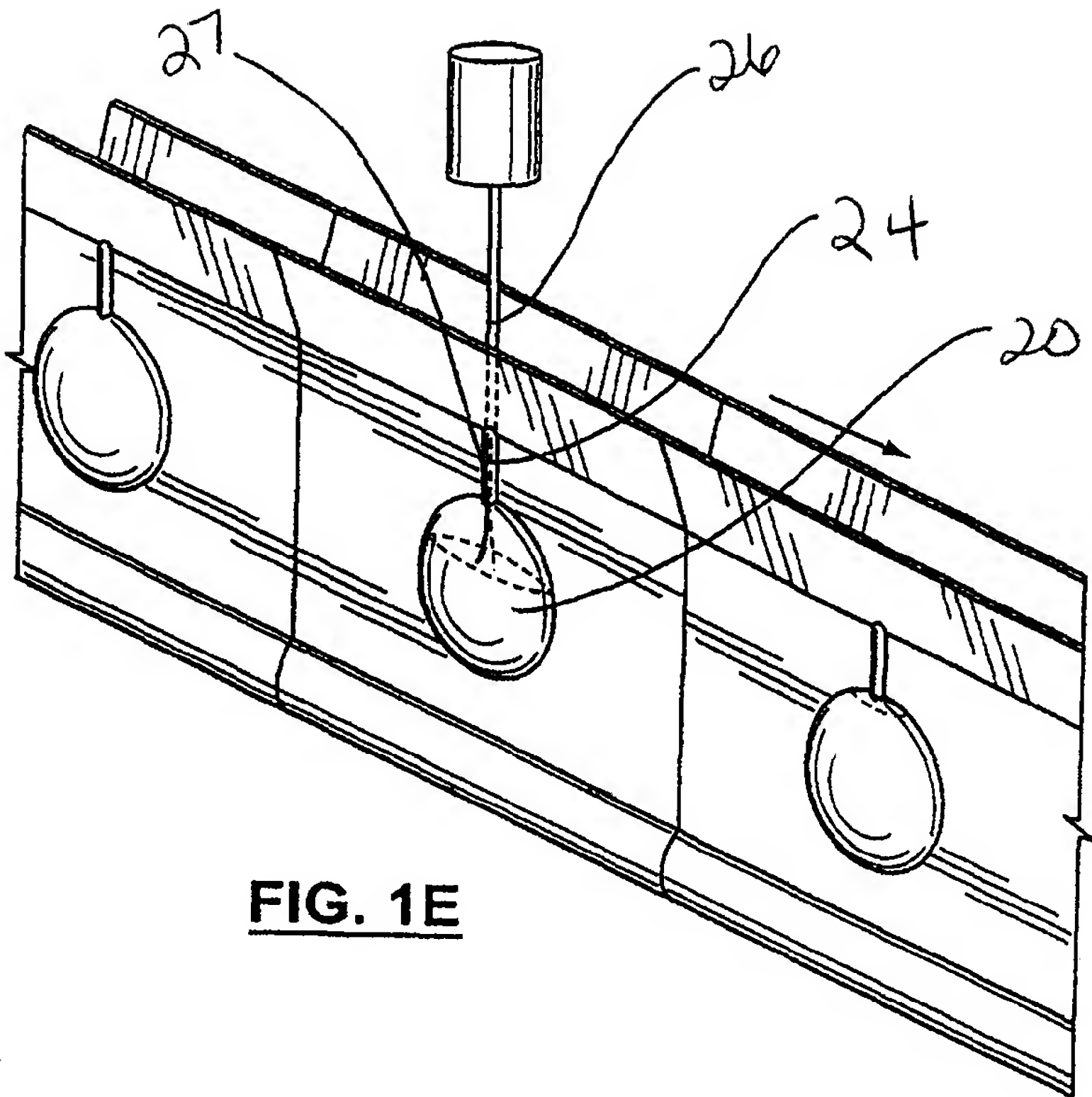


FIG. 1E

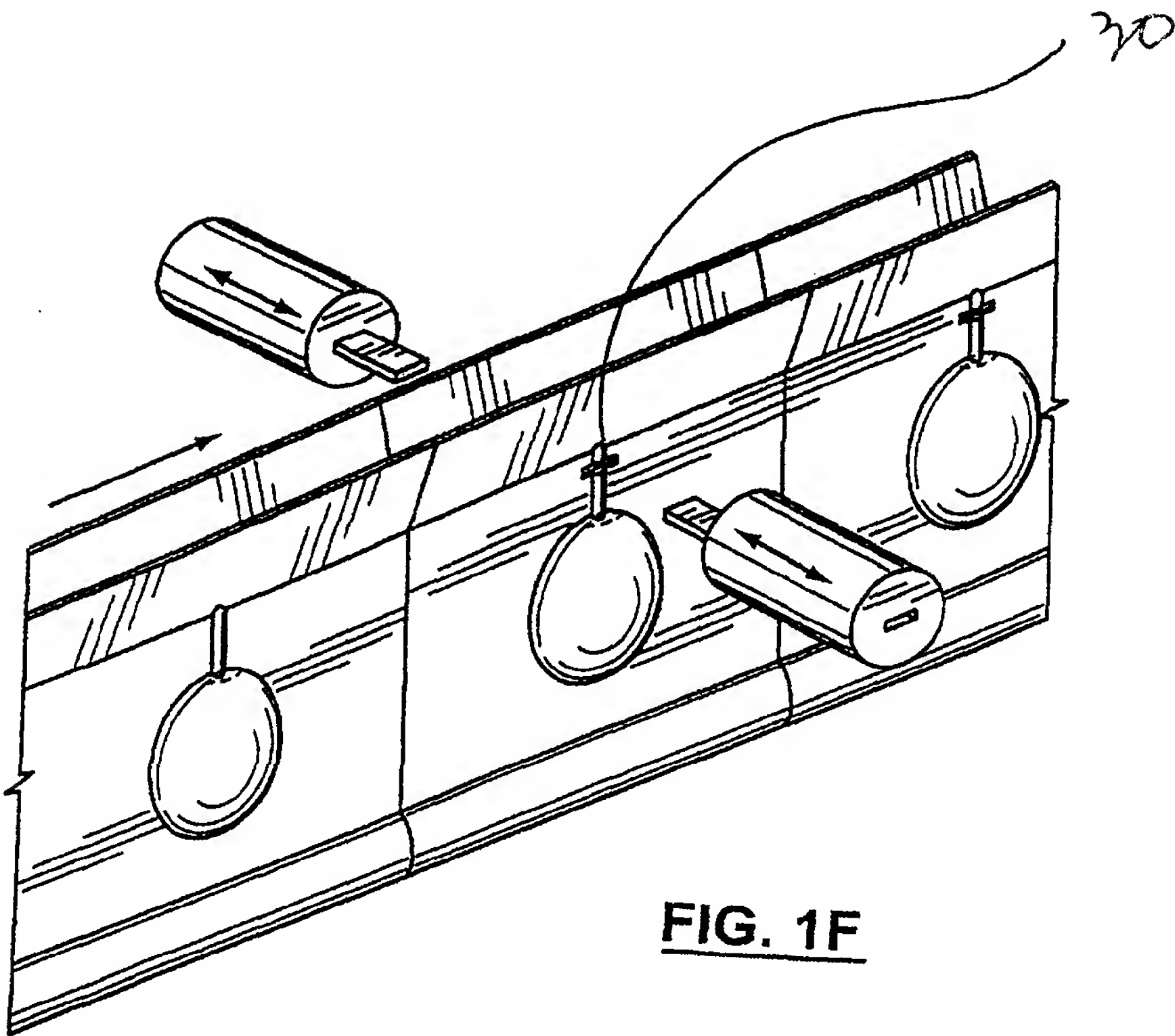


FIG. 1F

4/12

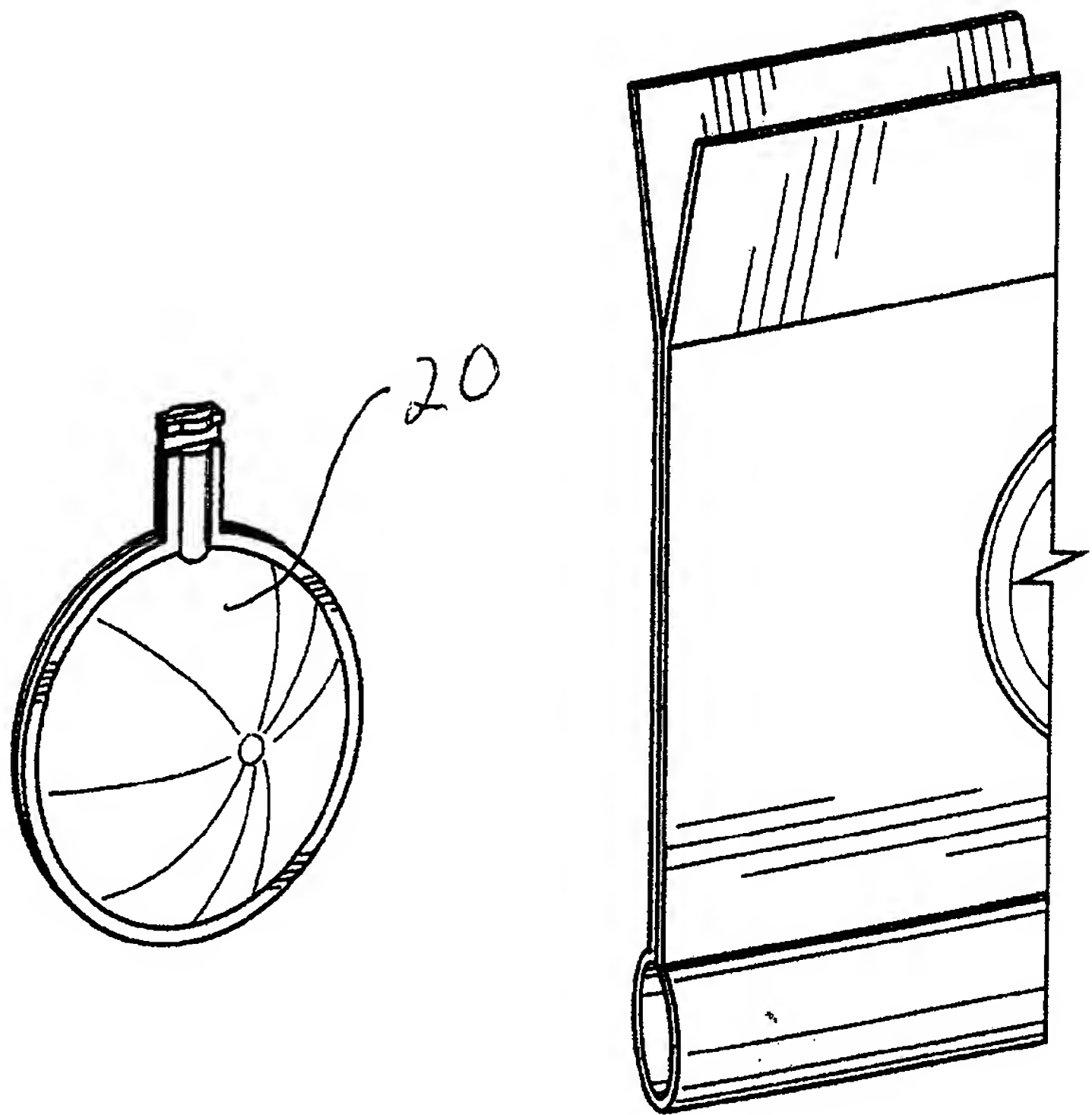


FIG. 1G

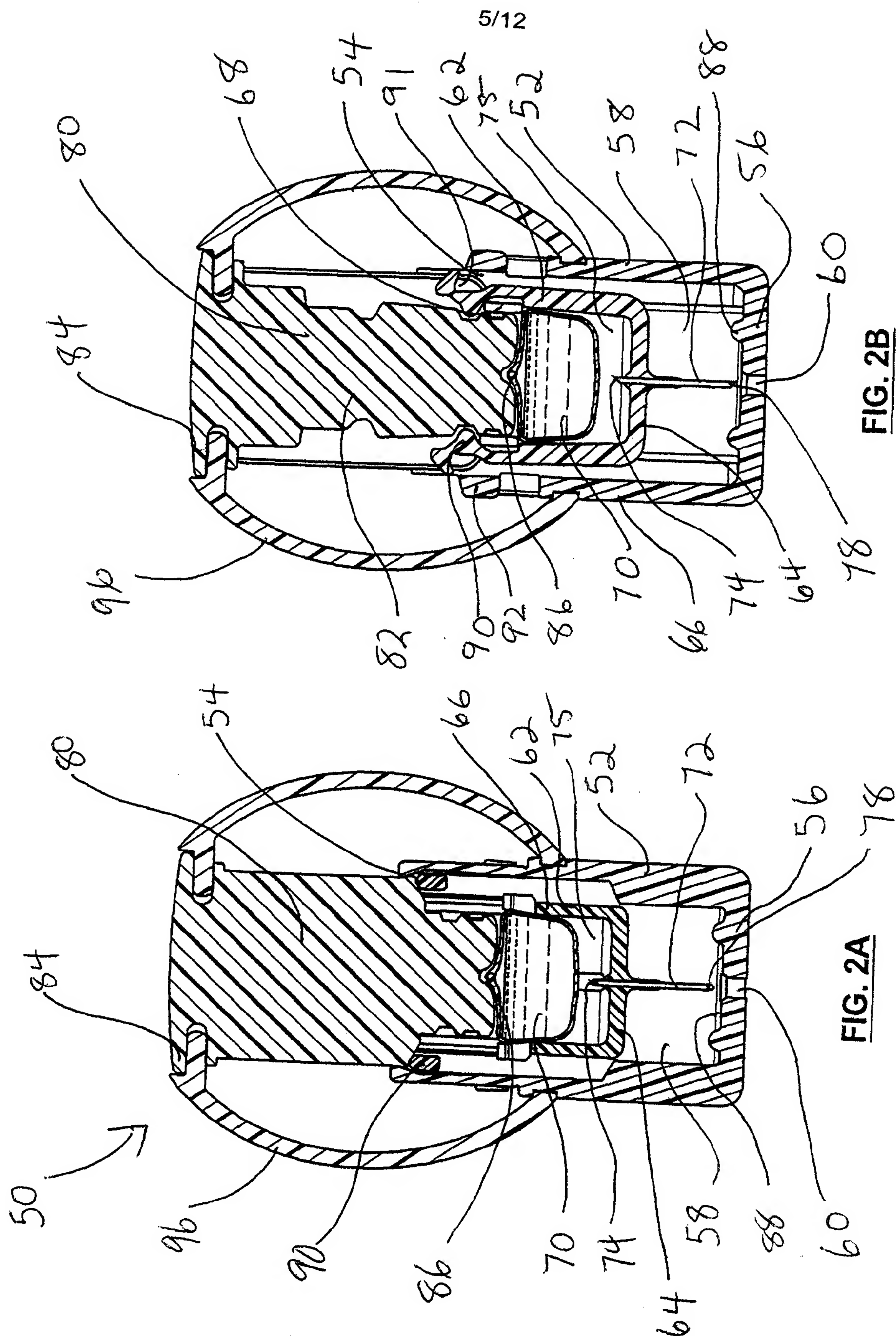
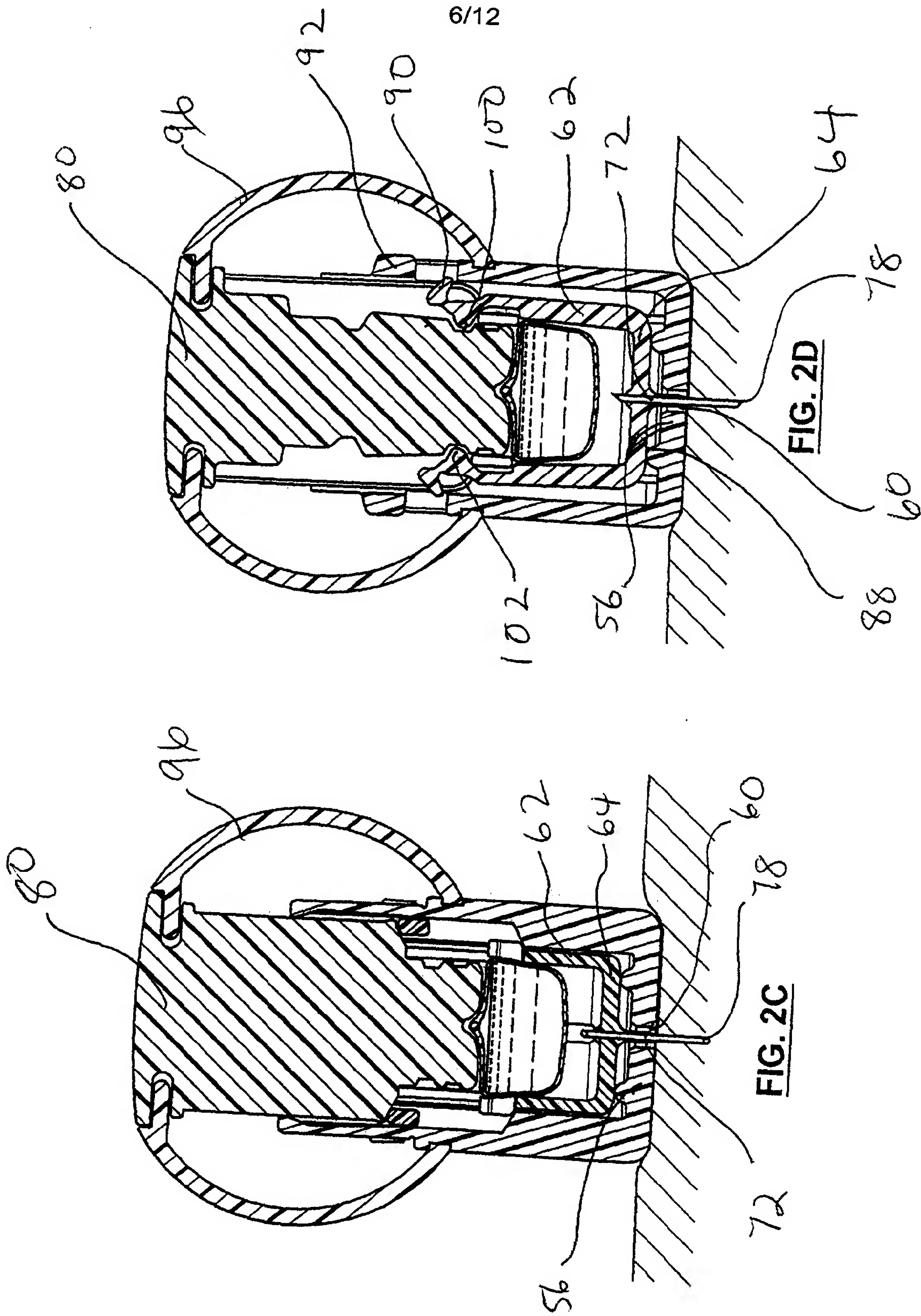


FIG. 2B

6/12



7/12

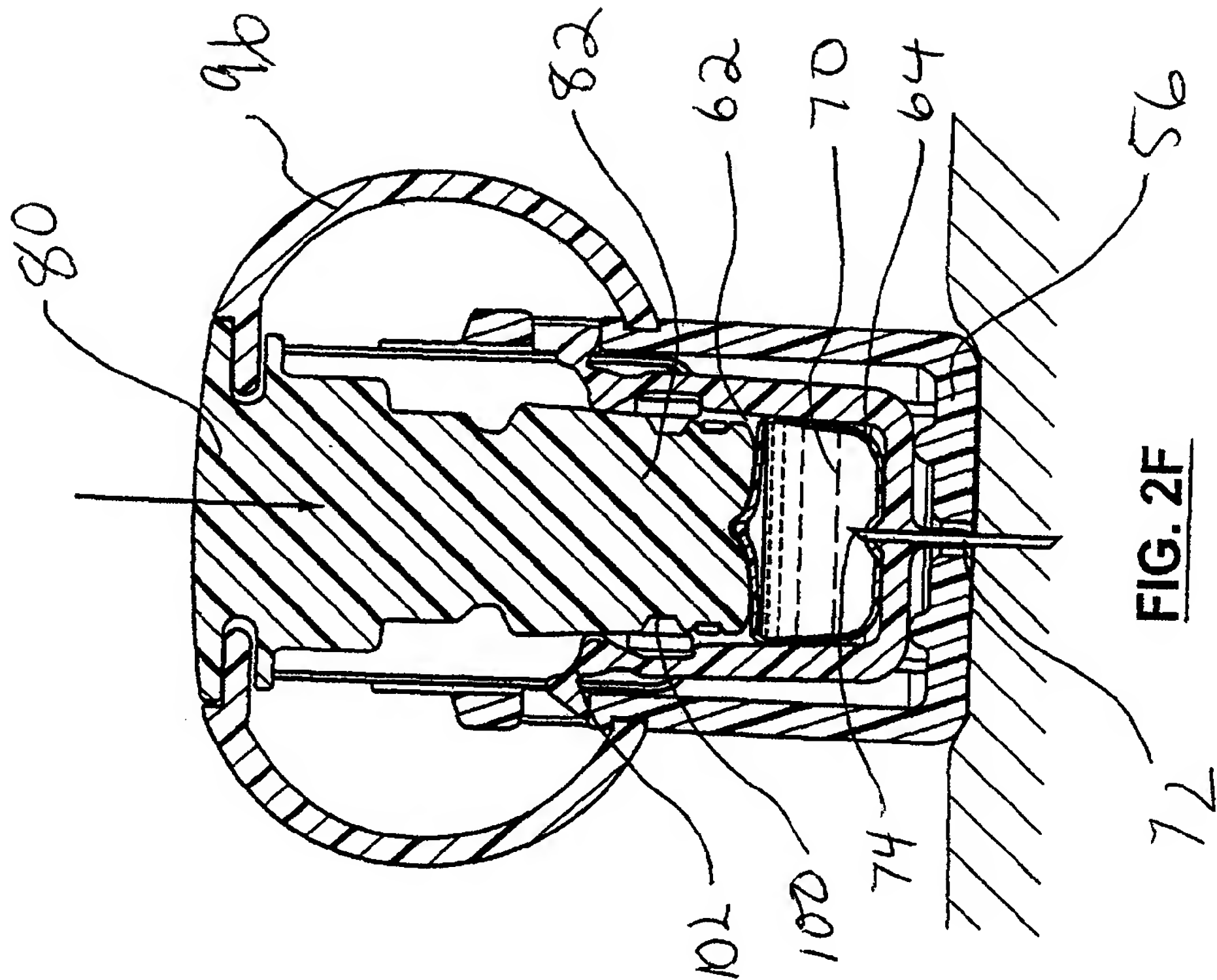


FIG. 2F

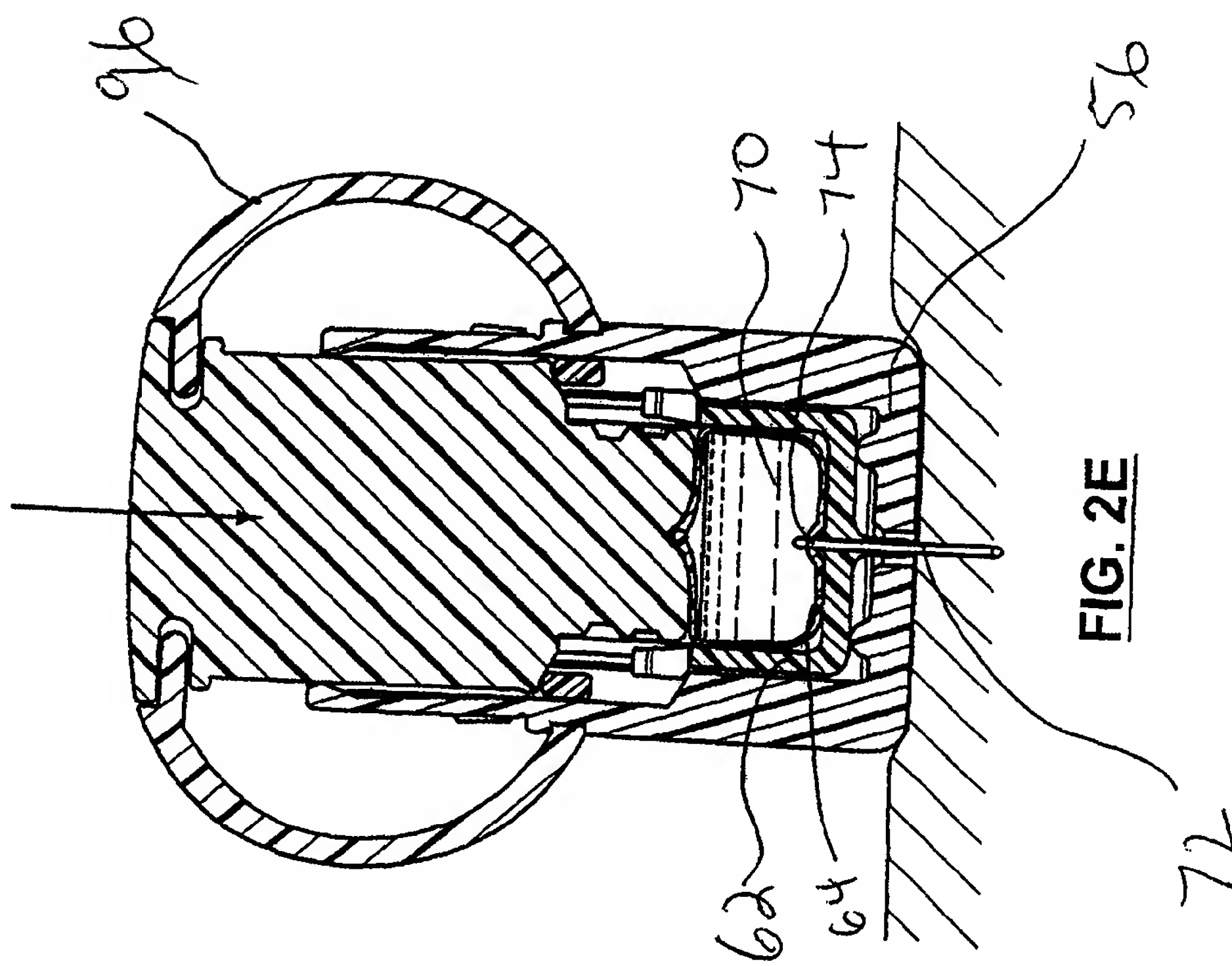
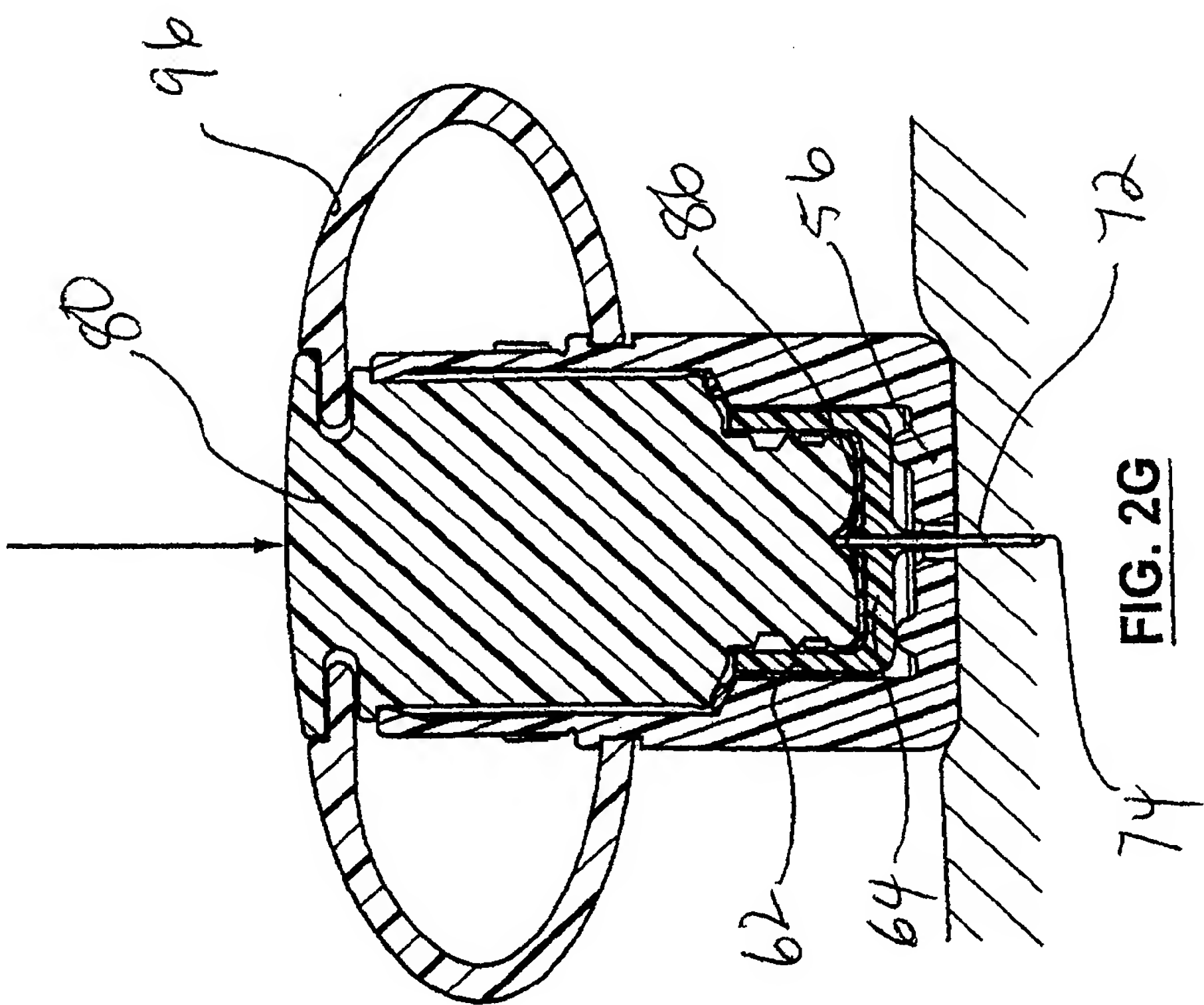
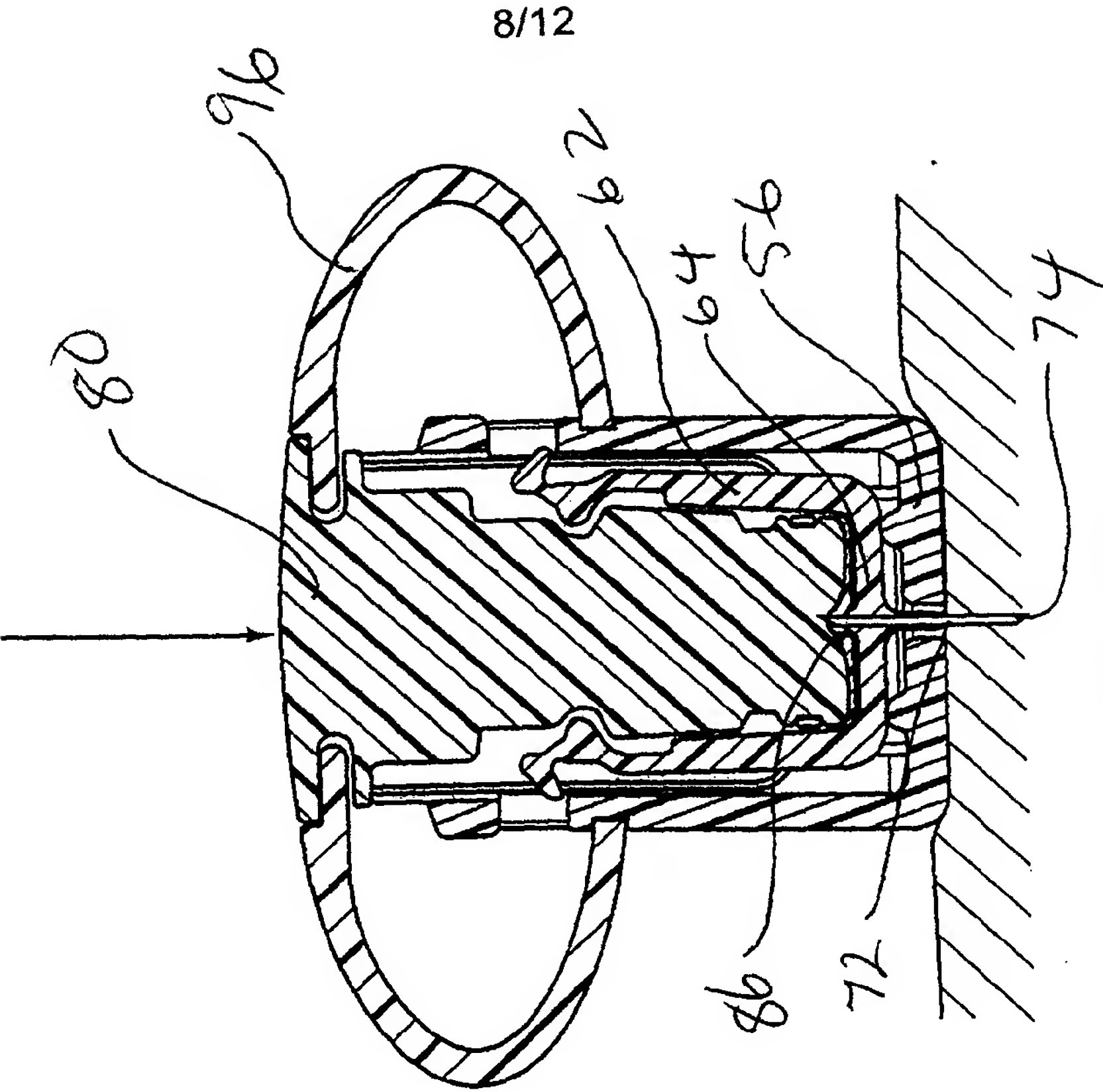


FIG. 2E



9/12

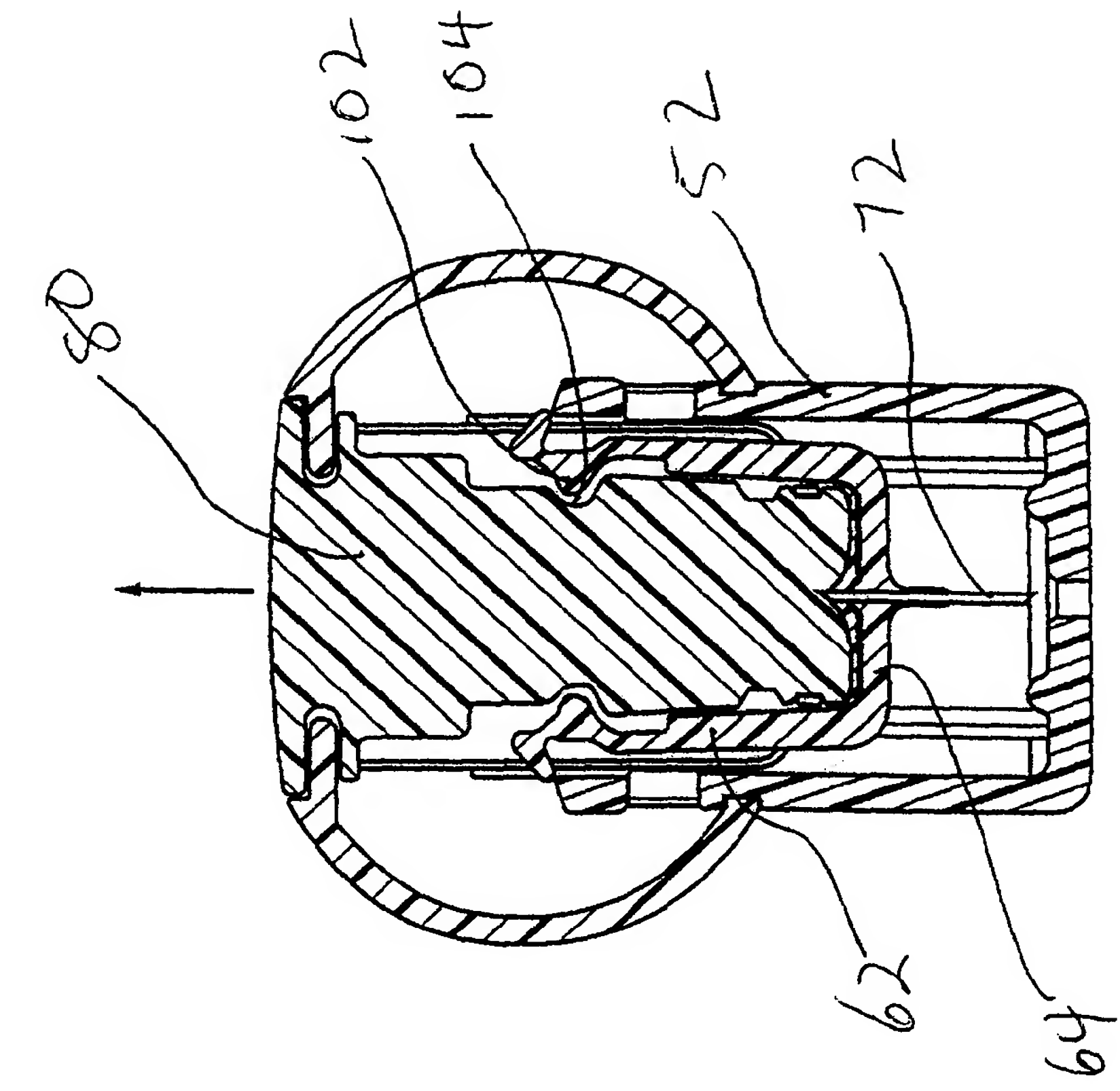


FIG. 2J

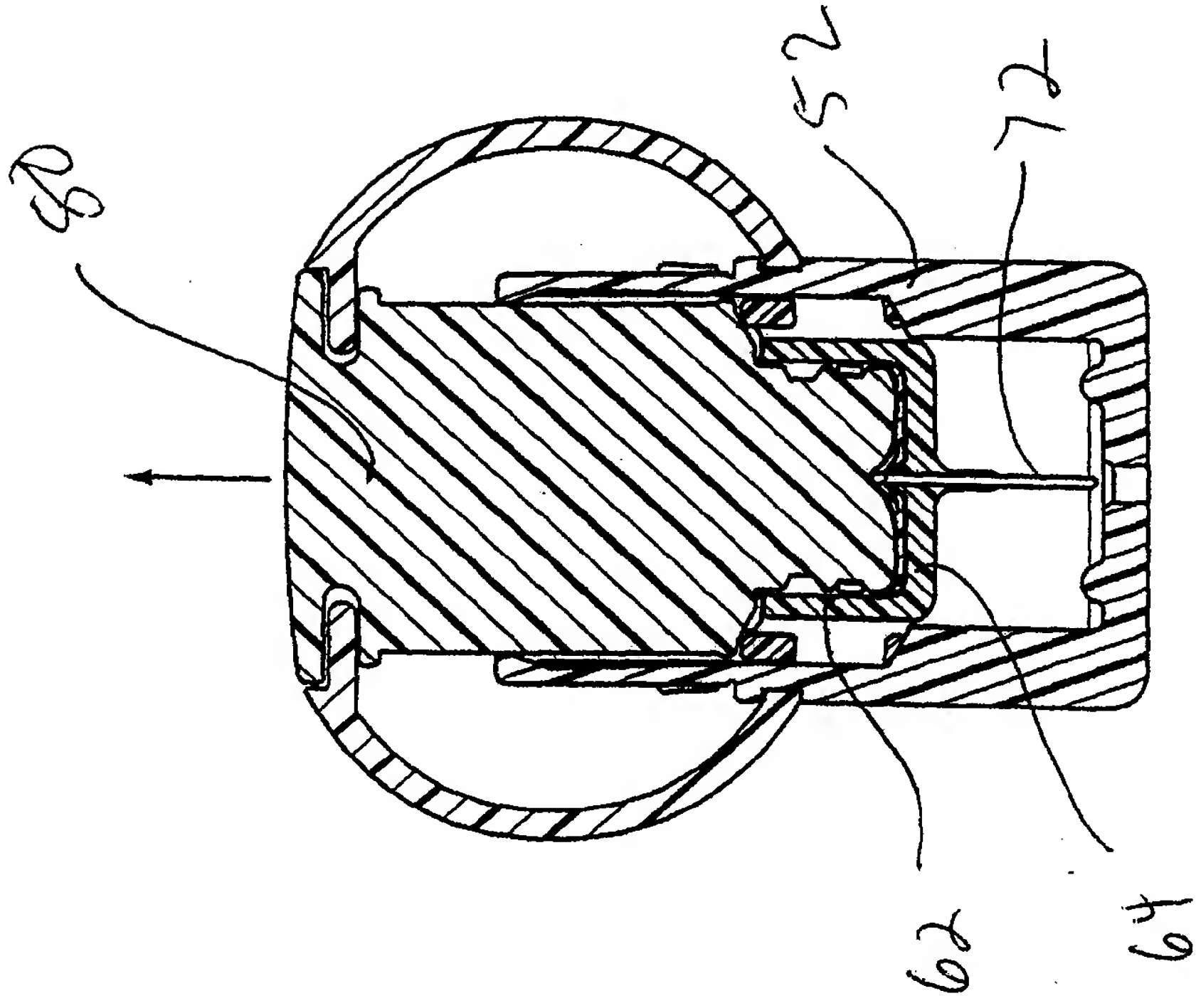


FIG. 2I

10/12

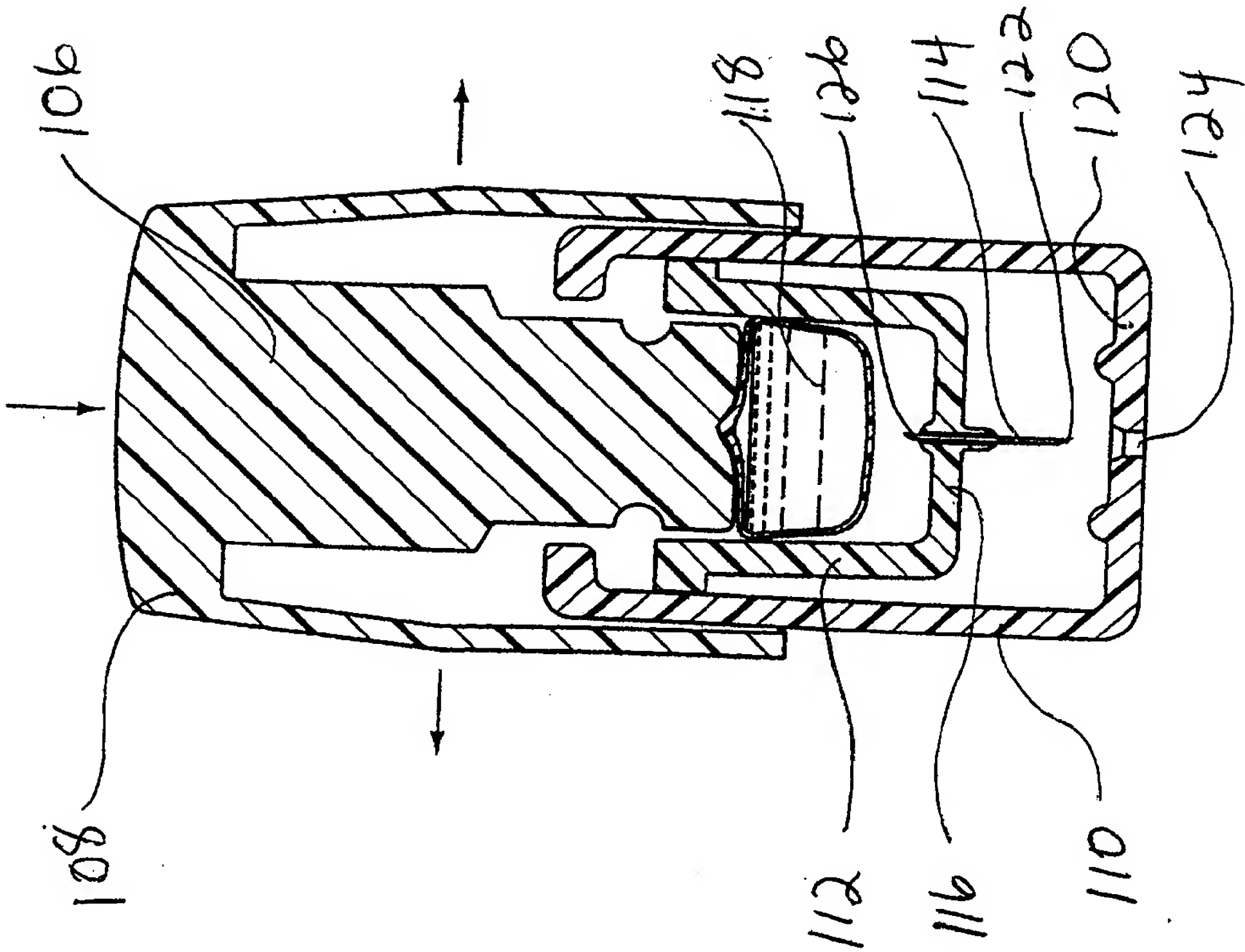


FIG. 3A

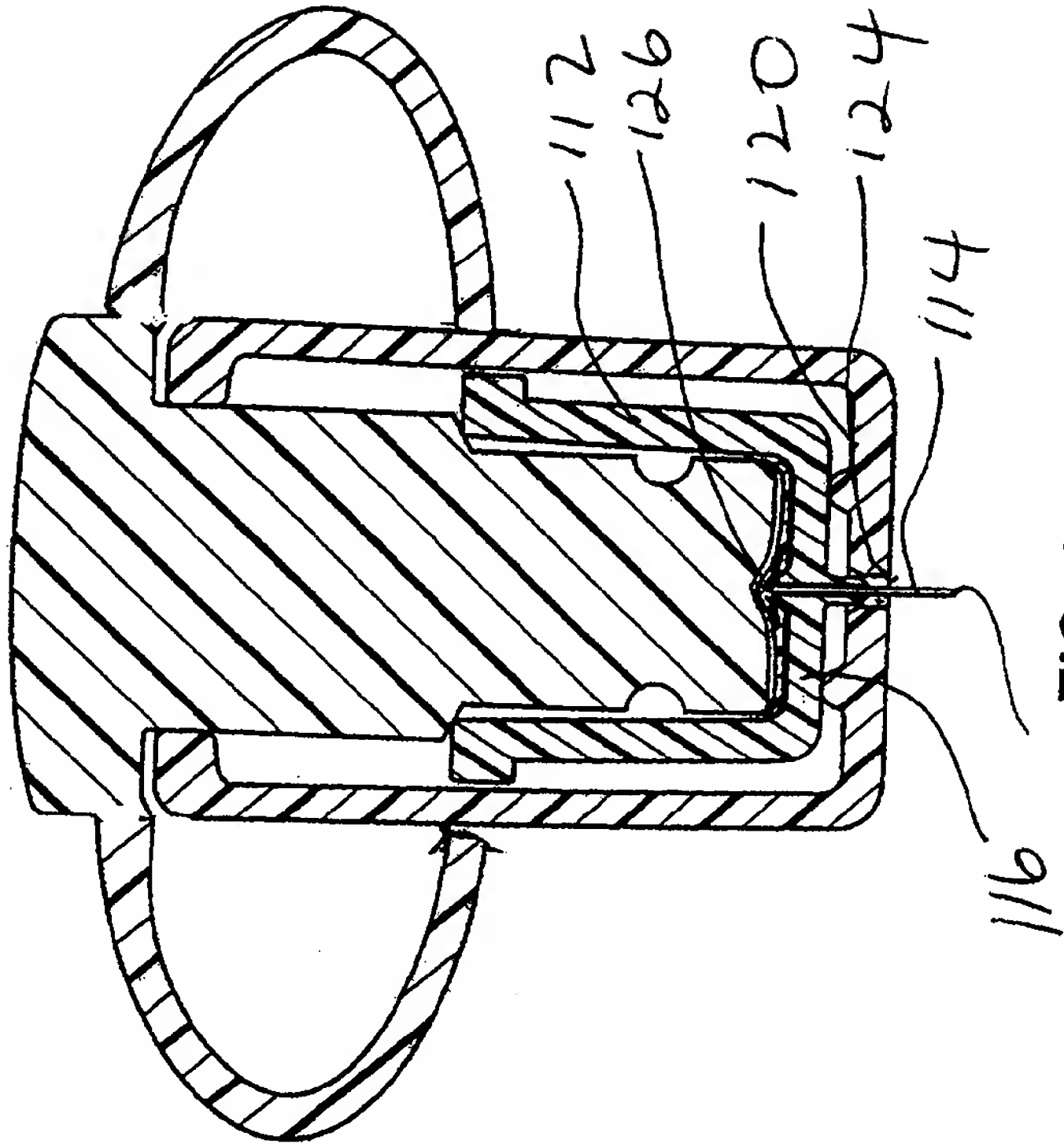


FIG. 3B

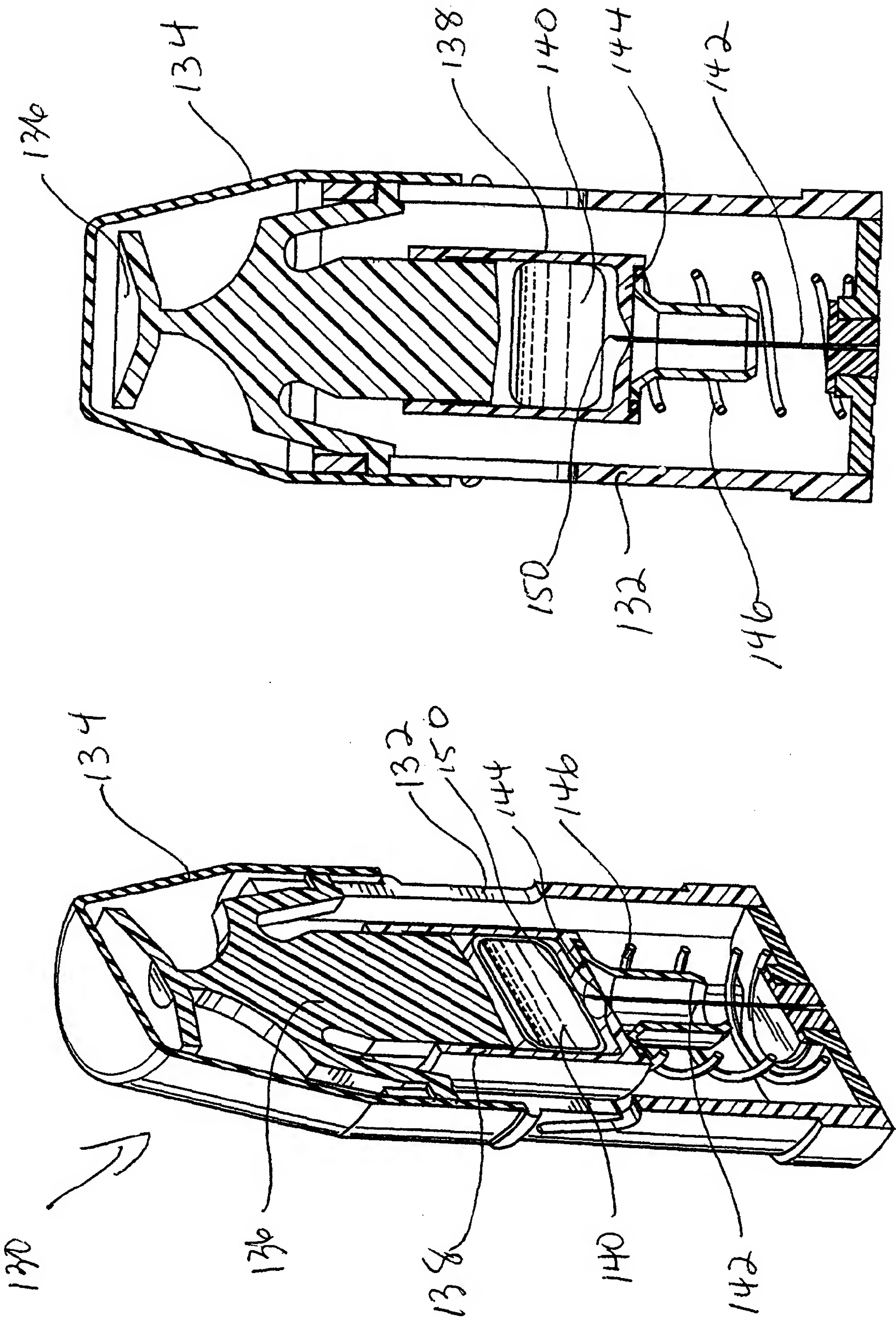


FIG. 4A

FIG. 4B

12/12

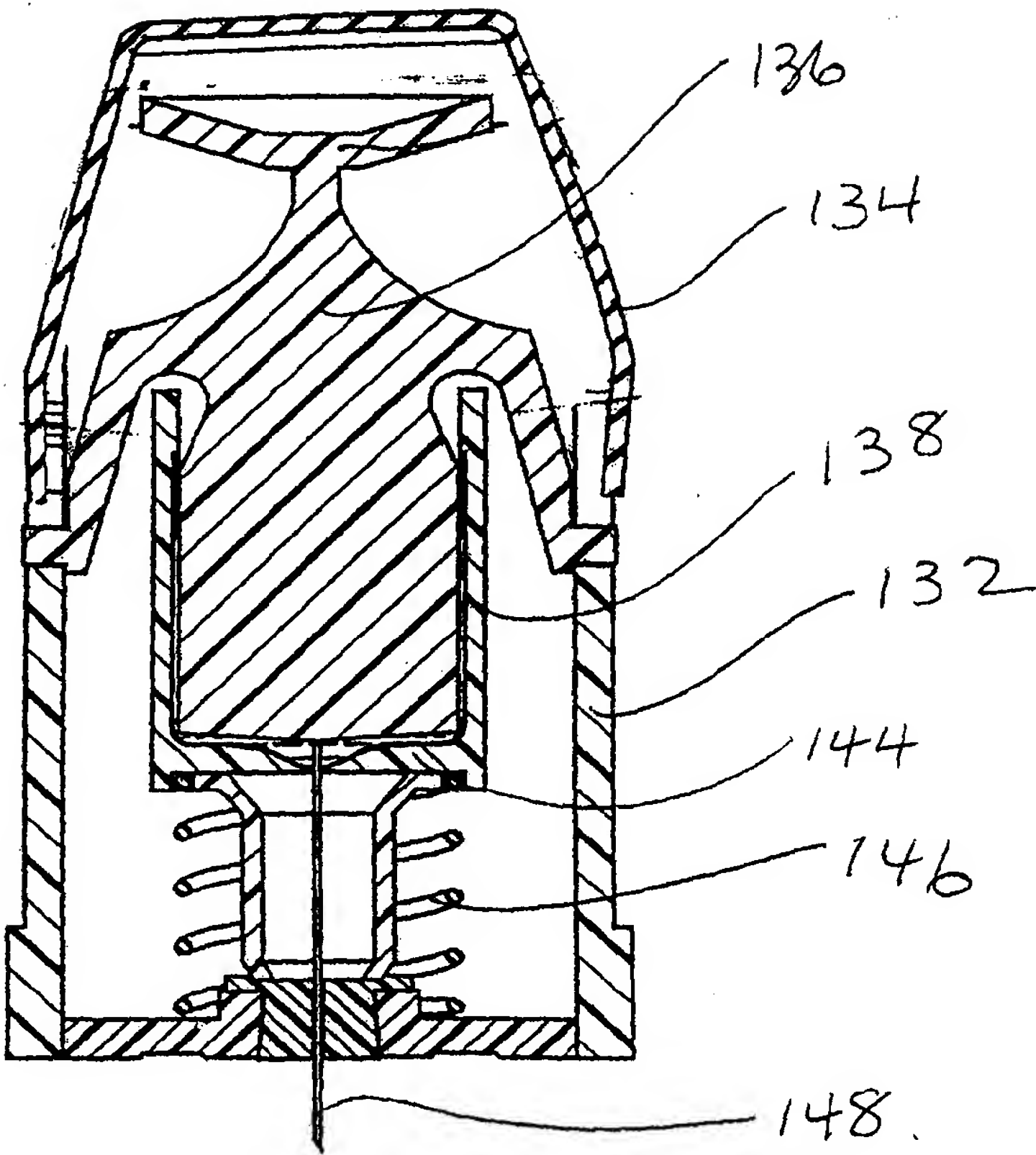


FIG. 4C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000225

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC: <i>A61J 1/10</i> (2006.01) , <i>A61M 5/00</i> (2006.01) , <i>A61M 5/178</i> (2006.01) , <i>A61M 5/46</i> (2006.01) According to International Patent Classification (IPC) or to both national classification and IPC</p>																							
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC: A61J-1/00; 1/05; 1/06; 1/10; 1/12; B65D*; A61M-5/145; 5/142;5/46 (2006.01) US Classification: 604/*</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) Canadian Patent Database; Delphion keywords: bladder, derm*, reservoir</p>																							
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X Y</td> <td>CA 2376147 A1 (CLARK ET AL.) 04 January 2001 (04-01-2001) refer to entire document</td> <td>1 to 5 2 to 5</td> </tr> <tr> <td>X Y</td> <td>CA 2328158 A1 (HOLMAN ET AL.) 28 October 1999 (28-10-1999) refer to entire document</td> <td>1, 3 to 7 2 to 5</td> </tr> <tr> <td>X Y</td> <td>EP 0330785 A2 (ROBBINS ET AL.) 06 September 1989 (06-09-1989) refer to entire document</td> <td>1, 3 to 5 2 to 5</td> </tr> <tr> <td>X Y</td> <td>US 3527215 A (DE WITT) 08 September 1967 (08-09-1967) refer to entire document</td> <td>1, 3 to 5 2 to 5</td> </tr> <tr> <td>X Y</td> <td>CA 2126320 C (RAKE ET AL.) 05 August 1993 (05-08-1993) refer to entire document</td> <td>1, 3 to 7 2 to 5</td> </tr> <tr> <td>X</td> <td>US 5997501 A (GROSS ET AL.) 07 December 1999 (07-12-1999) refer to figs. 15, 16 & 21; col. 13, line 19 to col. 15, line 13</td> <td>8 to 19 and 27 to 32</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X Y	CA 2376147 A1 (CLARK ET AL.) 04 January 2001 (04-01-2001) refer to entire document	1 to 5 2 to 5	X Y	CA 2328158 A1 (HOLMAN ET AL.) 28 October 1999 (28-10-1999) refer to entire document	1, 3 to 7 2 to 5	X Y	EP 0330785 A2 (ROBBINS ET AL.) 06 September 1989 (06-09-1989) refer to entire document	1, 3 to 5 2 to 5	X Y	US 3527215 A (DE WITT) 08 September 1967 (08-09-1967) refer to entire document	1, 3 to 5 2 to 5	X Y	CA 2126320 C (RAKE ET AL.) 05 August 1993 (05-08-1993) refer to entire document	1, 3 to 7 2 to 5	X	US 5997501 A (GROSS ET AL.) 07 December 1999 (07-12-1999) refer to figs. 15, 16 & 21; col. 13, line 19 to col. 15, line 13	8 to 19 and 27 to 32
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																					
X Y	CA 2376147 A1 (CLARK ET AL.) 04 January 2001 (04-01-2001) refer to entire document	1 to 5 2 to 5																					
X Y	CA 2328158 A1 (HOLMAN ET AL.) 28 October 1999 (28-10-1999) refer to entire document	1, 3 to 7 2 to 5																					
X Y	EP 0330785 A2 (ROBBINS ET AL.) 06 September 1989 (06-09-1989) refer to entire document	1, 3 to 5 2 to 5																					
X Y	US 3527215 A (DE WITT) 08 September 1967 (08-09-1967) refer to entire document	1, 3 to 5 2 to 5																					
X Y	CA 2126320 C (RAKE ET AL.) 05 August 1993 (05-08-1993) refer to entire document	1, 3 to 7 2 to 5																					
X	US 5997501 A (GROSS ET AL.) 07 December 1999 (07-12-1999) refer to figs. 15, 16 & 21; col. 13, line 19 to col. 15, line 13	8 to 19 and 27 to 32																					
<p>[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.</p> <table border="1"> <tbody> <tr> <td>* Special categories of cited documents :</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </tbody> </table>			* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family	"O" document referring to an oral disclosure, use, exhibition or other means		"P" document published prior to the international filing date but later than the priority date claimed										
* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention																						
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone																						
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art																						
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family																						
"O" document referring to an oral disclosure, use, exhibition or other means																							
"P" document published prior to the international filing date but later than the priority date claimed																							
<p>Date of the actual completion of the international search</p> <p>10 May 2007 (10-05-2007)</p>		<p>Date of mailing of the international search report</p> <p>18 May 2007 (18-05-2007)</p>																					
<p>Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476</p>		<p>Authorized officers</p> <p>Ishtiaque Ibne Rashid 819-953-0787 Kristian MacKenzie 819-934-4267</p>																					

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000225

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5931814 A (ALEX ET AL.) 03 August 1999 (03-08-1999) refer to entire document	8 to 19 and 27 to 32
X	EP 0652027 A1 (CIRELLI ET AL.) 10 May 1995 (10-05-1995) refer to entire document	8 to 19 and 27 to 32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000225

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 20 to 26

because they relate to subject matter not required to be searched by this Authority, namely :

According to **Article 17(2)(a)(ii)** and **Rule 39.1(iv)** of the **PCT**, International Search Authorities (ISAs) are not required to search any type of methods for treatment of the human or animal body by surgery or therapy (as well as diagnostic methods). Claims 20 to 26 relate to a method of administering a fluid drug through the skin of an animal, therefore an international search report and a written opinion have not been established on these particular claims.

2. ☐ Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. ☐ Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

Group A - Claims 1 to 7 are related to a reservoir for carrying an active agent, said reservoir comprising a fillable bladder of thermoplastic material.

Group B - Claims 8 to 19 and 27 to 32 are related to a device for delivery of a fluid drug to an animal.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2007/000225

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2376147 A1	04-01-2001	AU764881B B2	04-09-2003
		AU2929500 A	31-01-2001
		EP1194108 A1	10-04-2002
		GB2351272 A	27-12-2000
		NZ516257 A	25-07-2003
		US2002104856 A1	08-08-2002
		WO0100134 A1	04-01-2001
CA2328158 A1	28-10-1999	AU3399399 A	08-11-1999
		AUPP313398D D0	14-05-1998
		CN1298358 A	06-06-2001
		EP1097085 A1	09-05-2001
		JP2002513718T T	14-05-2002
		WO9954217 A1	28-10-1999
EP0330785 A2	06-09-1989	AU2671988 A	07-09-1989
		JP1254576 A	11-10-1989
		US4805799 A	21-02-1989
		US4925055 A	15-05-1990
US3527215 A	08-09-1970	AU445288B B2	04-02-1974
		AU1651670 A	23-12-1971
		BE752955 A1	16-12-1970
		DE2032908 A1	05-01-1972
		FR2097346 A5	03-03-1972
		GB1260108 A	12-01-1972
CA2126320 C	05-08-1993	AT237378T T	15-05-2003
		AT290897T T	15-04-2005
		AU729738B B2	08-02-2001
		AU1267997 A	24-04-1997
		AU2534897 A	10-10-1997
		AU3481993 A	01-09-1993
		BR9708126 A	18-01-2000
		CA2249236 A1	25-09-1997
		CN1218413 A	02-06-1999
		CZ294332 B6	15-12-2004
		DE69332877D D1	22-05-2003
		DE69332877T T2	22-01-2004
		DE69732779D D1	21-04-2005
		DE69732779T T2	06-04-2006
		DK624102T T3	14-07-2003
		DK929333T T3	20-06-2005
		EP0624102 A1	17-11-1994
		EP0929333 A1	21-07-1999
		ES2191661T T3	16-09-2003
		ES2236800T T3	16-07-2005
		HK1023731 A1	26-08-2005

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000225

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2126320 C (cont'd)	05-08-1993	HU9902680 A2	29-11-1999
		IL126207 A	31-10-2003
		IL156190D D0	23-12-2003
		JP5220204 A	31-08-1993
		JP7503162T T	06-04-1995
		JP2001513657T T	04-09-2001
		NO316969B B1	12-07-2004
		NZ331954 A	26-05-2000
US5997501 A	07-12-1999	AT142115T T	15-09-1996
		AT156375T T	15-08-1997
		AT220931T T	15-08-2002
		AU642112B B2	07-10-1993
		AU693136B B2	25-06-1998
		AU1076395 A	06-06-1995
		AU3632593 A	05-10-1993
		AU9058791 A	08-07-1992
		CA2074467 A1	14-06-1992
		CA2131794 A1	16-09-1993
		CA2176342 A1	26-05-1995
		DE69121881D D1	10-10-1996
		DE69121881T T2	03-04-1997
		DE69312916D D1	11-09-1997
		DE69312916T T2	08-01-1998
		DE69431066D D1	29-08-2002
		DE69431066T T2	27-02-2003
		EP0516783 A1	09-12-1992
		EP0630276 A1	28-12-1994
		EP0729366 A1	04-09-1996
		ES2176310T T3	01-12-2002
		IE75380 B1	10-09-1997
		IL111685 A	24-09-1998
		JP3442074B2 B2	02-09-2003
		JP5504711T T	22-07-1993
		JP7508427T T	21-09-1995
		JP9504974T T	20-05-1997
		NZ240875 A	27-04-1994
		NZ276485 A	24-11-1997
		US5156591 A	20-10-1992
		US5279544 A	18-01-1994
		US5527288 A	18-06-1996
		US5848991 A	15-12-1998
		WO9210234 A1	25-06-1992
		WO9317754 A1	16-09-1993
		WO9513838 A1	26-05-1995
		ZA9109794 A	26-08-1992
		ZA9301775 A	30-09-1993
		ZA9409185 A	25-07-1995

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/CA2007/000225

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US5931814 A	03-08-1999	AT163864T T	15-03-1998
		BR9504590 A	27-05-1997
		CA2159052 A1	29-04-1996
		CN1127660 A	31-07-1996
		DE59501597D D1	16-04-1998
		DK709104T T3	28-09-1998
		EP0709104 A1	01-05-1996
		ES2115305T T3	16-06-1998
		FI112439B B1	15-12-2003
		JP3715698B2 B2	09-11-2005
		TR960369 A2	21-06-1996
EP0652027 A1	10-05-1995	AT239522T T	15-05-2003
		AU696522B B2	10-09-1998
		AU7586994 A	11-05-1995
		CA2132277 A1	23-04-1995
		DE59410282D D1	12-06-2003
		DK652027T T3	25-08-2003
		HK1012590 A1	19-09-2003
		IL111316 A	30-11-1999
		JP3544715B2 B2	21-07-2004
		NZ264719 A	26-02-1998
		SG54173 A1	16-11-1998
		US5848990 A	15-12-1998
		ZA9408095 A	05-06-1995